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Noble metals in medicine: Latest advances

Serenella Medici[a,*], Massimiliano Peana[a], Valeria Marina Nurchi[b], Joanna I. Lachowicz[b], Guido Crisponi[b], Maria Antonietta Zoroddu[a,*]

[a] Department of Chemistry and Pharmacy, University of Sassari, Via Vienna 2, 07100 Sassari, Italy
[b] Department of Chemical and Geological Sciences, University of Cagliari, Cittadella Universitaria, I-09042 Monserrato, Cagliari, Italy

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Abbreviations: AAgM, aliargentumycine, silver(I)-tartaric acid; AMPZ, $[\{cis\text{-}Pt(NH_3)_2\}_2(\mu\text{-}OH)(\mu\text{-pyrazolate})]^{2+}$; aspH, *o*-acetylsalicylic acid; Auranofin, (1-thio-beta-D-glucopyranosato)-(triethylphosphine)goldl-2,3,4,6-tetraacetate; Bipy, 2,2′-bipyridine; Bzac, benzoylacetonate; Carboplatin, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II); Cisplatin, *cis*-diamminedichloroplatinum(II); COD, 1,5-cyclooctadiene; Dmf, dimethylformamide; Dmso, dimethylsulfoxide; Dox, doxorubricine; Dppm, 1,1-bis(diphenylphosphino)methane); en, ethylenediamine; ER, endoplasmic reticulum; G1, growth 1 phase; G2/M, growth 2/M phase; GSH, glutathione; HCT116, human colorectal cancer cells; HeLa, Henrietta Lacks cancer cells; HeLa-S3, Henrietta Lacks cancer cells S3 type; Hep-G2, hepatocellular carcinoma cells; HAS, human serum albumin; MIC, minimum inhibitory concentration; MMP, mitochondrial membrane potential; NHC, N-heterocyclic carbene; HIV, human immunodeficiency virus; HMGB1, high-mobility group protein B1; *o*-HbzaH, *o*-hydroxy-benzoic acid; *p*-HbzaH, *p*-hydroxy-benzoic acid; 2-hepy, 2-(2-hydroxyethyl)pyridine; Hptab, *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexakis(2-pyridylmethyl)-1,3,5-tris(aminomethyl)benzene); IC50, half maximal inhibitory concentration; Iproplatin, dichlorodihydroxybis(2-propanamine)platinum; KP1019, *trans*-[tetrachlorobis(1H-indazole)ruthenate(III)]; KTZ, ketoconazole; Lobaplatin, 1,2-diammino-methyl-cyclobutaneplatinum(II)-lactate; MMP, mitochondrial membrane potential; mtDNA, mitochondrial DNA; NAMI-A, *trans*-[tetrachloro(DMSO)(imidazole)ruthenate(III)]; Nedaplatin, diammine[(hydroxy-κO)acetato(2-)-κO]platinum NHC *N*-heterocyclic carbene; NPs, nanoparticles; *o*-HbzaH, *o*-hydroxy-benzoic acid; Oxaliplatin, [(1*R*,2*R*)-cyclohexane-1,2-diamine](ethanedioato-*O*,*O*′)platinum(II); p53, tumor protein p53; *p*-HbzaH, *p*-hydroxy-benzoic acid; PAMAM, poly(amido amine); Ppy, 2-phenyl-pyridine; Phen, 1,10-phenanthroline; Picoplatin, *cis*-amminedichloro(2-methylpyridine) platinum(II); PPh_3, tpp triphenylphosphine; R&D, research and development; PTA, 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane; RAPTA-C, $[(\eta^6\text{-}p\text{-cymene})Ru(II)(PTA)Cl_2]$ ROS reactive oxygen species; Satraplatin, bis(acetato)amminedichloro(cyclohexylamine)platinum(II); Sac, saccharinate; SCC, silver carbene complexes; SCK, shell crosslinked nanoparticles; SOD, superoxide dismutase; Terpy, 2,2′ ;6′,2″-terpyridine; T-47D, solid human breast ductal carcinoma; TrxR, thioredoxin reductase; Tpms, tris(pyrazol-1-yl)methanesulfonate; *Trans*platin, *trans*-diamminedichloroplatin; TSC, thiosemicarbazone.

* Corresponding authors. Tel.: +39 328 8270495
E-mail addresses: sere@uniss.it (S. Medici), zoroddu@uniss.it (M.A. Zoroddu).

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ABSTRACT

History shows that metal-based drugs and remedies have been known and used since very ancient times. For example, silver was employed in the treatment of wounds and ulcers according to the Greek physician Hippocrates, but its antimicrobial properties had probably been recognized long before because it was used to make vessels for storing liquids in pure form. The ancient Egyptians also knew how to sterilize water with copper. The medical use of gold can be dated back to 2500 B.C. in China. However, the new era of metal-based medicine started almost 50 years ago when cisplatin was shown to inhibit cellular division in *Escherichia coli*, thereby leading to the first studies of its antitumor activity in rats and its assessment as one of the most powerful drugs for use against different types of cancer, although many other novel metal-based drugs are promising and they are attracting growing attention in modern clinical medicine. Gold salts and arsenic compounds have been in use for decades in the treatment of rheumatoid arthritis and syphilis, respectively, but studies of cisplatin have definitely shifted the attention of researchers to the pool of transition "heavy" metals as potential therapeutic agents. Rhodium, iridium, palladium, osmium, and the other so-called noble elements have been the subjects of intensive investigations, thereby leading to the production of a series of complex compounds with remarkable anticancer activities, as well as antirheumatic, antimalarial, and antimicrobial drugs. The number of published studies in this field is huge and they have already been the subjects of careful review. In this review, we provide a detailed account of the latest results (2010–2013) and their potential uses in the cure of severe diseases.

1. Introduction

Among all the elements in the periodic table, transition metals are some of the most versatile in terms of their applications related to human progress, conquest, war, and art, because bronze and iron brought us out of the Stone Age. However, when we think of the "noble metals," we instinctively conjure images of wealth and power, such as coins, jewels, and precious and expensive works of art. More recently, this class of elements has found a wide range of application from the aerospace and electronic industries to health.

The documented history of noble metal-based drugs started with the chance discovery of cisplatin (*cis*-diamminedichloroplatinum(II)) [1,2] as one of the most powerful chemotherapeutic agents against ovarian and testicular cancer, although gold salts had been tested against tuberculosis and were employed as antirheumatics in 1929 [3]. Since then, a vast library of metal complexes has been synthesized and applied in the pharmacological field, mostly as anticancer agents, but also as anti-inflammatory, antibacterial, antirheumatic, and antimalarial drugs. In particular, they have many applications against tumors, which are based mainly on the strong interactions between metals and DNA, although other molecular targets have been proposed such as thiol-containing proteins and redox processes.

The colloidal state is another form in which noble metals are used as therapeutics, such as silver and gold nanoparticles. Although their effectiveness is still under debate and some doubts have been raised about their safety, colloidal gold, silver, iridium, ruthenium, and rhodium are sold widely and they are readily available on the Internet as panaceas to combat many diseases, free radicals, and bacteria.

Therefore, it is time to consider the new developments in this fascinating field and this review provides a detailed account of the latest results.

2. Platinum

Platinum should be the starting point because cisplatin represents the first use of metal complexes in medicine. There have been many studies of this compound and its variants (Fig. 1) (carboplatin,

oxaliplatin, satraplatin, and picoplatin, but nedaplatin, lobaplatin, and eptaplatin are used more widely in Asia), thus we provide some useful references instead of repeating well-known details [4–10]. By contrast, we focus on recent efforts to improve the performance of cisplatin. Indeed, although this drug is still the lead compound used against various types of cancer (especially ovarian, testicular, bladder, neck, and small cell lung cancer), its activity is restricted to a limited spectrum of tumors and the drug itself has a series of clinical disadvantages.

Systemic toxicity is one of the main issues. The primary cisplatin target is DNA [11,12] in both sick and healthy cells, without distinction, in the same manner as most antineoplastics. However, due to the affinity of platinum for the sulfur and selenium donors present in many proteins in the plasma and in the cellular milieu, cisplatin can interact and disrupt the functions of different proteins and enzymes, as demonstrated by the fact that only 1% of the intravenously administered drug actually reaches DNA. This produces a variety of severe side effects, such as nephro-, hepato-, oto-, and neurotoxicity, gastrointestinal disturbances, bone marrow suppression, hair loss, and anemia. Pt(IV) octahedral complexes (such as iproplatin and satraplatin) exhibit reduced reactivity toward these biomolecules and lower toxicity due to their relative inertness compared to Pt(II) compounds. Thus, they have been proposed as prodrugs based on an "activation by reduction" mechanism that leads to Pt(II) active species [10]. Pt(IV) complexes with carboxylate axial ligands are absorbed better by the gastrointestinal tract than their divalent analogues and they have good potential as orally administrable platinum drugs (satraplatin).

A second consideration is that cisplatin may induce resistance. Cisplatin can bind DNA via both interstrand and intrastrand cross-linking, thereby hindering RNA transcription and DNA replication, and subsequently triggering cell death pathways [13]. However, its efficacy is frequently lost after several chemotherapy cycles because tumor cells become resistant. The mechanism that allows resistance to develop is still a matter of debate and three possible suggestions are the enhancement of DNA repair pathways, detoxification of the drug (e.g., inactivation by glutathione (GSH)), or changes in the uptake and efflux of the drug, which could also operate synergically [14]. It is clear that platinum drugs that bind DNA in the same manner and create the same kind of adduct as cisplatin (e.g., carboplatin) will probably induce cross-resistance to cisplatin. Different strategies have been adopted to overcome this problem [9]. *Cis* Pt(II) compounds with sterically hindered amines (e.g., picoplatin) still form DNA adducts in a similar manner to cisplatin, but their interaction with thiol-containing molecules is less effective, which can counteract the adaptive increase in the detoxification pathways mediated by GSH and metallothioneins. Moreover, *trans* Pt(II) complexes are now receiving new acceptance as antitumor drugs after a long period when they were overlooked because early evidence suggested that *trans*-diamminedichloroplatin had no therapeutic effect compared with its *cis* stereo-isomer. However, substitution of the two ammonia ligands with a variety of amines flanked by N-donor heterocyclic ligands produced active *trans* compounds that can bind DNA with significant toxicity [9]. Those bearing two acetate groups instead of chlorides, as well as bulky aromatic ligands, were found to be effective against cisplatin-resistant cancers. A different approach to circumvent resistance employs polynuclear Pt(II) compounds where two or more platinum centers are linked by aliphatic polyamine ligands (spermine, spermidine, etc.) (Fig. 2). These types of complexes can bind DNA in a different manner compared with cisplatin and its analogues, thereby causing more extended damage and hairpin loops, which may be more difficult to repair by the proteins responsible for this task [9]. Cationic polynuclear Pt(II) complexes can interact with DNA via noncovalent binding. They have high positive charges and they exhibit

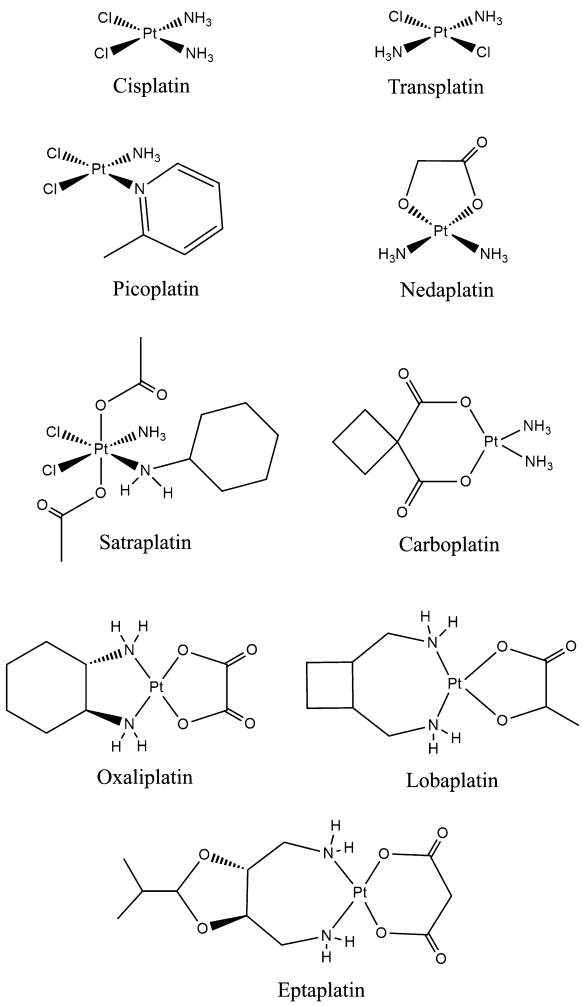


Fig. 1. Platinum-based chemotherapeutic agents.

electrostatic (non-coordinative) pre-associations with negatively-charged biomolecules (such as DNA) before developing coordinative interactions.

A third issue is the fact that cisplatin only reaches DNA in low amounts (the majority is dispersed within the plasma and the cells) and its lack of selectivity. Much effort has been made to develop carriers that can increase the availability of the drug via a better transport system (nanotubes, nanoparticles, or micelles) or its selective delivery into tumor cell (hormones), thereby sparing the healthy cells, particularly by derivatizing Pt(II) species or Pt(IV) prodrugs in an appropriate manner.

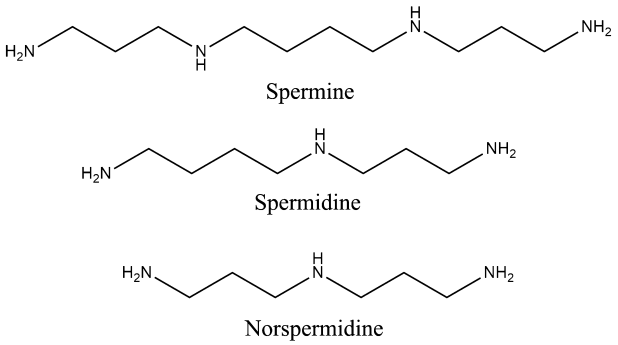


Fig. 2. Aliphatic polyamine ligands.

Finally, new platinum complexes with a wide range of ligands or ligand combinations are being synthesized continuously to improve the performance of cisplatin, but also to find a completely different alternative to cisplatin itself, which could be a matter of sheer luck, as every researcher knows.

2.1. Trans-Pt(II) derivatives

Trans-platinum complexes are being evaluated as potential antitumor drugs because of their interesting proprieties, which extend beyond the mere interaction between the metal species and DNA [15], as reported for *trans*-Pt(II) complexes that bear aliphatic amines and that target different proteins [16]. Transplatin derivatives where one of the canonical NH_3 ligands is substituted with N-based aromatic heterocycles (such as pyridines, thiazoles, or quinolines) exhibit comparable cytotoxicity to cisplatin but almost no cross-resistance. Their activity has been studied based on more labile leaving groups (e.g., carboxylates) and their interactions with different types of DNA have been elucidated, thereby demonstrating that cooperation among different structural modifications leads to DNA damage [17]. Pyridines seem to be a more efficient alternative to NH_3 in transplatin derivatives. A *trans*-Pt(II)-chloride complex with a substituted pyridine ligand, 2-(2-hydroxyethyl)pyridine (2-hepy), was synthesized and its cytotoxicity was evaluated. *Trans*-$[PtCl_2(2\text{-hepy})_2]$ exhibited a higher anticancer activity compared with transplatin, cisplatin, carboplatin, and oxaliplatin [18]. Analogous systems with 2-hydroxyalkyl-pyridines in the *trans* configuration rather than a saccharinate or a pyridine-2-carboxylate ligand exhibited lower efficacy but they were active [19,20]. Another *trans*-configured Pt(II) complex with oxime ligands, *trans*-$[PtCl_2(Me_2C{=}NOH)_2]$, was found to be up to 20 times more potent than cisplatin, depending on the cancer cell lines tested [21]. Indeed, one of the most interesting applications of *trans* complexes uses sulfonamide ligands. Sulfonamides have been employed as antibiotics, anticonvulsants, and as inhibitors of different enzymes. A series of *trans*-Pt(II) mono-sulfonamide complexes was assessed to compare their antiproliferative activities with that of cisplatin using a panel of representative human tumor cells. They exhibited much higher activities than cisplatin, which depended on the structure of the sulfonamide ligand, on the cell line tested, and, interestingly, on the halide used as the anionic ligand (chloride versus iodide). The stereochemistry of chiral sulfonamides has also been considered, which showed that at least one tumor line was more sensitive to a specific enantiomer compared with another [22].

2.2. Polynuclear Pt(II) complexes

A new azolato-bridged dinuclear Pt(II) complex, $[\{cis\text{-}Pt(NH_3)_2\}_2(\mu\text{-OH})(\mu\text{-pyrazolate})]^{2+}$ (AMPZ), was found to exhibit markedly higher toxic effects in some tumor cell lines than conventional mononuclear cisplatin. For the first time, using this system, it was demonstrated that small conformational distortions induced by AMPZ in highly polymeric DNA with a random nucleotide sequence are corrected by DNA repair systems less efficiently than those induced by cisplatin [23]. This can improve the antitumor effects of these new metallodrugs in cancer cells given that a tetrazolato-bridged dinuclear platinum(II) complex also has a markedly high in vivo antitumor activity against pancreatic cancer, thereby indicating that these compounds are potentially active against cisplatin-nonresponsive tumors [24].

Evidence of a similar disruptive effect on DNA but via a more complex mechanism was obtained for a tridentate trinuclear Pt(II) complex, $[Pt_3Cl_3(hptab)]^{3+}$ (hptab = *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexakis(2-pyridylmethyl)-1,3,5-tris(aminomethyl)benzene), which has remarkable cytotoxic effects in human and mouse tumor cells, including those resistant to conventional cisplatin [25]. This study aimed to elucidate the coordination capabilities of $[Pt_3Cl_3(hptab)]^{3+}$ toward DNA and found that, in the absence of other biological targets, it can form trifunctional intrastrand crosslinks with the duplex. Instead, in the presence of proteins, as is the case in the cellular environment, this complex crosslinks proteins to DNA. Furthermore, when a macromolecular crowding agent is added to mimic the environmental conditions in the cell nucleus, the Pt_3 species crosslinks two DNA duplexes with a high yield, where this feature was observed for the first time in antitumor trinuclear platinum complexes [25]. Other dinuclear complexes with aromatic diamines and picoline derivatives have been tested against ovarian and breast cancers, where they yielded comparable or higher cytotoxicity than cisplatin, but the induced cellular responses differed from those caused by the lead drug [26,27].

Finally, it is important to report the evaluation of mixed multinuclear Ru(III)/Pt(II) complexes as potential antimetastatic and antineoplastic agents. The results obtained in breast and non-small cell lung cancers are encouraging and they open up new perspectives in this area [28–32].

2.3. Pt(II) and Pt(IV) passive carriers

The frequently poor absorption of Pt-based drugs by the gastrointestinal tract is an important issue that affects their bioavailability. Thus, intravenous administration is required, although the amount of drug that reaches the target DNA is still very limited. Moreover, like most antineoplastic agents, platinum does not distinguish between healthy and diseased cells. Thus, derivatization of the Pt-drug with appropriate carriers is a research area that is attracting considerable interest, both for helping the active species cross the cellular membrane and/or for selectively entering tumor tissues. The targeting and delivery strategies are based on two types of mechanism: passive and active transport inside tumor cells. A wide range of nanocarriers (nanoparticles, nanotubes, nanomicelles, liposomes, and polymers) have been evaluated to address the first issue [10,33–37] by exploiting their physicochemical properties (such as the unique shape of nanotubes, which promotes cellular uptake and allows the functionalization of bioactive molecules on their surfaces) and the biological differences between normal and neoplastic cells to increase selectivity. This approach is based on permeability and retention effects, where macromolecules exhibit increased permeability in tumor tissues so they can accumulate due to low lymphatic clearance and slow venous return [38,39]. Platinum complexes have relatively low molecular weights and they cross the membranes of normal and cancerous tissues rapidly, while it has been noted that micelles and polymeric carriers are selectively concentrated in tumors when they are grafted to liposomes [39]. The appropriate (nanoscale) size of the carrier molecules should be selected carefully because this is the factor that prevents their migration into healthy tissues and their elimination by renal clearance. This mechanism can be improved further by attachment to drug transporters, antigens, or receptors that can bind selectively to tumor-specific moieties displayed by the target cells.

2.4. Pt(II) active carriers

Some tumors can be sensitive to hormones, such as estrogens and progesterone in some breast and ovarian cancers, and testosterone in prostate cancer. These molecules bind to receptors on the tumor cells, thereby causing changes in the expression of specific genes, which may lead to the stimulation of cell growth. This mechanism can be exploited to help platinum drugs enter neoplastic tissues with higher efficacy and selectivity. Androgens [40],

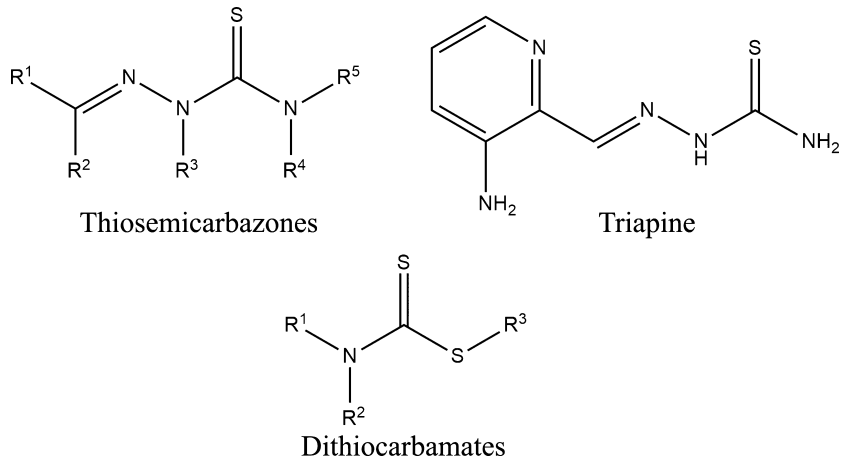


Fig. 3. General formulas for two of the most used ligands in metal-based anticancer drugs, together with an example of effective thiosemicarbazones (triapine).

testosterone derivatives [41], estradiol [42–45], and lipophilic ethisterone [46] have been used to derivatize Pt complexes, thereby obtaining better performance in terms of both efficiency and targeting compared with the traditional reference metallodrugs. Other molecules, including carbohydrates, bisphosphonates, peptides, and proteins, have been used as carriers with different results [10]. Tumor cells exhibit increased glucose metabolism and glucose dependence, which may provide another route into these tissues, thus polysaccharides have been investigated from this perspective [47].

2.5. Pt(II) compounds with antitumor drugs

Associating the platinum center with drugs that already possess anticancer properties is a good way of enhancing their activity, which is often higher in their bound state. For example, thiosemicarbazones (TSCs) are a class of compounds with relevant biological properties (antiviral, antifungal, antibacterial, antitumor, anticarcenogenic, and insulin-mimetic). In particular, the 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine, Vion Pharmaceuticals, New Haven, CT) is currently being screened to determine its antitumor effects using the National Cancer Institute panel of 60 tumor cell lines, and it has been selected for Phase I and II clinical trials [48–52] (Fig. 3). The antineoplastic activity of TSCs is attributable only to the inhibition of ribonucleotide reductase, which is an enzyme involved in the rate-limiting step of DNA synthesis. In addition, the presence of sulfur (soft) and nitrogen (hard) donors allows coordination with metal ions, thereby making them very versatile ligands. This ability to chelate metals has now been recognized as the reason for their antiproliferative action. Furthermore, the redox activity of Fe-TSC complexes is crucial for their anticancer activity by causing oxidative damage and the inhibition of ribonucleotide reductase [53] and DNA topoisomerase IIR [54–57]. Thus, TSCs with different derivatives have been used to prepare platinum complexes with high cytotoxicity, low nephrotoxicity, and good efficacy against normal and resistant cancer lines [58–63], and they are interesting candidates as anticancer therapeutics.

Other Pt(II) complexes have been prepared with a series of antitumor agents, such as podophyllotoxin [64], camptothecin [65], and endoxifen [66], all of which obtained good results in terms of their high cytotoxicity and DNA cleavage capabilities.

2.6. Pt(II) complexes with DNA-intercalating molecules

DNA binding with metallointercalators results in a covalent interaction, which causes disentanglement of the double helix to facilitate π-stacking interactions between the ring cloud of the base pairs and the intercalating planar aromatic systems. Although research into this subject dates back to the pioneering work of Lippard and co-workers in the late 1970s, many platinum complexes with pyridines [20], bipyridines [67], terpyridines [68], phenanthrolines [67,69,70], naphthalene [71], anthraquinones [72], and their derivatives continue to be synthesized and tested to assess their possible anticancer activity, effectiveness in DNA binding, DNA cleavage, and telomerase inhibition activity.

2.7. Mitochondria targeting

This is one of the new areas for chemotherapy treatments because damage to mitochondria causes irreversible cell death or apoptosis. Like nuclear DNA, mitochondial DNA (mtDNA) is sensitive to platinum drugs, which can be delivered to these organelles via carbon nanostructures [73–75] or appropriately functionalized peptides [76,77], where mtDNA damage is sufficient to mediate the activity of a platinum-based chemotherapeutic by inducing apoptosis but without damaging nuclear DNA.

2.8. Pt(IV) compounds activated by visible light

Pt(IV) complexes are normally less cytotoxic than their divalent counterparts, so they are considered to be pro-drugs and they are assumed to provide Pt(II) active species via a mechanism known as “activation by reduction.” However, this is not always the case [78]. New and interesting Pt(IV) pro-drugs include those activated by light, which generally have a *trans* configuration, and they bear two amines (also mixed) [79], two imines [80], two azido ligands [81–83], or a mixed diazido-amine system [84]. They are normally inactive or slightly active in the dark, but they are selectively activated under UV and/or visible light. Their efficiency is increased by replacing one or two NH_3 ligands with pyridine [80], which can reach up to 50–65 times that of cisplatin when measured in the same conditions [84]. It has been demonstrated that light at the appropriate wavelength will cause the dissociation of one or more ligands, thereby giving different active Pt(II) photoproducts, but rarely Pt(IV) species. The formation of a cytotoxic azydil radical has also been suggested for complexes containing the azide ion. Their mechanisms of action are still under study, but DNA appears to be the target involved most often, where its damage cannot be recognized by HMGB1 protein, in contrast to cisplatin-type lesions [84]. Cell death via non-apoptotic pathways has also been recognized [83].

2.9. Different activities

Most of the applications of platinum and other metal-based drugs are focused on cancer treatment, but much research has addressed treatments for different diseases and health problems.

In particular, the antibacterial activity of platinum complexes is often evaluated together with that of palladium complexes. For example, Pt(II) and Pd(II) derivatives of benzothiazoline ligands have both been tested against fungal (*Fusarium oxysporum* and *Alternaria alternata*) and bacterial strains (*Pseudomonas aeruginosa* and *Escherichia coli*), which showed that the two metal complexes had similar activities [85]. Pt(II) and Pd(II) dithiocarbazate complexes containing triphenylphosphine as the coligand were evaluated against *Trypanosoma cruzi*, and they had a considerably higher activity compared with the reference compound used for the treatment of the pathology related to this parasite [86].

In addition, an interesting platinum complex with a quinoline ligand, which could be used orally, decreased amyloid plaques in the brain tissue of transgenic mouse models affected by Alzheimer's disease [87].

3. Palladium

cis-$[(CH_3CH_2O)_2(bzac)_2Ti(VI)]$ was the first non-platinum complex employed in clinical trials against a vast range of ascites and solid tumors [88,89]. Subsequently, the race began to find the successor to cisplatin, with reduced toxicity and applicability to a wider spectrum of cancers by using an extraordinarily wide range of ligands and metals.

The coordination chemistry of Pd(II) is very similar to that of Pt(II), thus the choice of this metal in the search for a valid alternative to cisplatin appeared straightforward. However, it was only 15 years ago that a real interest in its anticancer activity started to begin among researchers, but this interest is still increasing judging from the amount (considerably more than one hundred) of published studies since.

Pd(II) complexes differ from those of platinum in several respects. First, they exhibit a greater propensity to exchange their ligands, i.e., about 10^5 times higher than Pt(II). This can cause the rapid hydrolysis of palladium-based drugs. The ligand dissociation generates very active species that can easily interact with donor species encountered in the bloodstream and cellular environment, thereby preventing the drug from reaching its target. Thus, while platinum complexes can be therapeutically active, the corresponding palladium complexes are generally inactive, but toxic because of their higher reactivity. This process can be avoided by using bulky chelating ligands, thereby achieving higher stabilization with a strongly coordinated ligand (e.g., an N-containing donor), which should be coupled to a careful choice of leaving group(s) (reasonably nonlabile) in order to ensure that the in vivo structural integrity of the compound is retained for a sufficiently long period to achieve its therapeutic action. Another feature is that palladium predominantly forms *trans* isomers and some Pd(II) compounds transform spontaneously into inactive *trans* derivatives, while a *cis* configuration with Pt-drugs exhibited higher anticancer activity on average.

In addition, an advantage of Pd-compounds is their higher solubility compared with platinum.

Pd(II) complexes have been reported to have cytotoxic activity against human cervical epitheloid carcinoma, human chronic myelogenous leukemia, osteogenic sarcoma, malignant melanoma, breast cancer, lung cancer, glioma, human colorectal adenocarcinoma, head and neck squamous cancer, prostate cancer, and ovarian cancer [90–99].

The structural variety of Pd(II) compounds that have been synthesized recently as antitumor drugs is dominated by sulfur-containing ligands, such as TSCs and thiocarbamates (Fig. 3), nitrogen-based heterocycles (pyridines, bipy, terpy, phenanthrolines, and quinolines), saccharinate derivatives, or their combinations. Furthermore, polyamines that form polynuclear complexes have been employed. Some of these Pd(II) complexes exhibit higher activity than their Pt(II) analogues, as well as greater activities than cisplatin and other approved Pt drugs.

3.1. Pd(II) complexes with thiosemicarbazones

As mentioned previously, TSCs possess relevant biological properties against viruses, bacteria, and cancer. In particular, compounds where the TSC side-chain bears an *N*-heterocyclic ring in the α position, i.e., α-*N*-heterocyclic TSCs, have good antineoplastic activities and a strong propensity to chelate metals. Thus, their association with a transition ion should enhance their activity, as found in some Pd(II) complexes of TSCs, which were more active than the ligand alone, and they are antiproliferative agents with activities comparable to or higher than cisplatin, even at low micromolar concentrations, as well as against resistant tumor cells or in cisplatin-nonsensitive cancers (e.g., breast cancer) [100].

In the Pd(II) complexes tested for use as anticancer drugs, the TSC ligands form mono- [101] or bis-chelated species [102], or they are flanked by other ligands such as planar *N*-heterocycles [103], phosphines [102,104–106], and even arsines [107]. TSCs may be derivatized with planar *N*-heterocycles [100,108] to exploit the intercalative properties of the planar aromatic moiety, especially in resistant cancers. In addition to being evaluated as antitumor drugs, most of these complexes have interesting antimicrobial properties.

3.2. Pd(II) complexes with dithiocarbamates

For many years, dithiocarbamates have been tested to assess their efficiency as inhibitors of cisplatin-induced nephrotoxicity, which can be caused by platinum binding and the inactivation of thiol-containing enzymes. Dithiocarbamates can efficiently coordinate to transition metals and their Pt(II) and Pd(II) complexes exhibit high anti-tumor activities, as well as reduced toxicity, compared with cisplatin and analogous compounds. Thus, it is thought that the strong bonds of platinum or palladium with dithiocarbamate may block metal interaction with sulfur-containing renal proteins, thereby preventing, or at least reducing, their nephrotoxicity. Furthermore, Pd(II) mixed ligand dithiocarbamate-amine complexes have antitumor activities that are comparable to cisplatin, but without cross-resistance [109,110].

A number of mixed-ligand Pd(II) complexes have emerged during the past few years, where the second ligand is normally an *N*-heterocycle [111–113] or a phosphine [114], and they have obtained promising results, often at lower doses than cisplatin.

3.3. Pd(II) complexes with saccharinates

Saccharine, or its better known anionic form saccharinate, has a good affinity for a number of transition metal ions. A new trend in anticancer research is to use this ligand in association with *N*-heterocycles, such as pyridines and terpyridines, to obtain effective drugs against a variety of tumors. Studies have demonstrated that these complexes can induce apoptosis and necrosis, as well as cleaving DNA in the cancer cells tested [115–118,90,119].

3.4. Multinuclear Pd(II) complexes

Di- and trinuclear Pt(II) complexes have been synthesized to cause more extended damage to DNA, thereby preventing any

repair mechanism from inducing resistance in cancer cells treated with cisplatin and its analogues, and polynuclear Pd(II) complexes with polyamines have been prepared and evaluated in different cancer lines. Although they appear to be promising agents both in vitro and in vivo compared with many platinum-based anticancer drugs, none of these compounds has yet entered clinical trials. It is generally agreed that the mode of action of Pd(II) complexes as cytotoxic agents is similar to that described for their structural Pt(II) analogues, but it is unlikely that the structure-activity relationships of the latter can be extended successfully to Pd(II) systems. Thus, due to the differences in their reactivity, a more detailed study has still to be undertaken to clarify all the different aspects of the interactions of polynuclear Pd(II) complexes with DNA.

Spermine is the most widely used diamine ligand, and its Pd(II) dinuclear complexes exhibit good properties against breast cancer and resistant ovarian carcinoma [120,121]. Their mechanism of interaction with DNA is still under study [122] but it has been shown that the interaction is specific, where they induce the distortion and local denaturation of the B-DNA structure with the release of some guanine bases. The DNA strands partially open up and allow the formation of palladium intra- and interstrand cross-links, then leading to the production of DNA adducts and aggregates.

In addition, norspermidine (Fig. 2) and its trinuclear Pd(II) complexes have been considered because of their antineoplastic potential. In fact, norspermidine is a naturally occurring triamine in some species of plants, bacteria, and algae, but not in humans, and it has antineoplastic activities against different types of tumors in mice. It was demonstrated that this complex was more effective than its Pt(II) counterpart, where it caused growth inhibition and cell death in different cancer cell lines. Furthermore, both norspermidine and its Pd(II) complex decreased the number of colonies of breast cancer lines, thereby indicating that these compounds reduced the malignancy of breast cancer cells [123].

3.5. Different activities

In terms of the different activities of palladium complexes in addition to anticancer effects, it is known that palladium complexes of isonicotinamide have higher activity against *Mycobacterium tuberculosis* than isonicotinamide and pyrazinamide alone [124]. The search for new anti-tuberculosis drugs is a major concern at present because this disease appeared to have been defeated a couple of decades ago when life conditions, wealth, and good healthcare systems had worked to eradicate it, but it has now gained new vigor as a consequence of the impact of migration fluxes. Moreover, the treatment of tuberculosis is long and it should be uninterrupted, otherwise resistance can be induced in the bacteria. Rifampicin, which was discovered more than 50 years ago, represents the last novel class of antibiotics introduced for the first-line treatment of tuberculosis. Treatments are based on a 6-month regimen, which is ineffective against multi-drug and extensively drug-resistant tuberculosis, as well as being incompatible with many antiretroviral drugs. Although investments in R&D strategies have increased substantially in recent decades, the number of new pharmaceuticals approved by drug regulatory agencies worldwide has not increased correspondingly. Pd(II) compounds with new steroidal TSCs have been tested against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium*, and *E. coli*, and they exhibit remarkable antibacterial activities compared with amoxicillin [125]. Palladium was also used to prepare related complexes of some antibiotic drugs, such as capreomycin, kanamycin, and ofloxacin. These compounds were evaluated to assess their activities against tuberculosis using both the *M. tuberculosis* strain and infected THP-1 (human leukemia) cell lines. The results showed that these complexes had extracellular activities that were comparable to those of their parent drugs and improved efficacy against intracellular infection with *M. tuberculosis* [126].

A totally different use of palladium in medical practice is the application of the ^{103}Pd isotope in so-called brachytherapy, which is an internal radiotherapy used for different types of cancer (mainly cervical, prostate, breast, and skin cancer). ^{103}Pd is a radiation source that may be placed inside or next to the area requiring treatment. Recently, this strategy was also applied in ophthalmology for the treatment of T3- and T4-staged choroidal melanomas [127,128].

4. Ruthenium

Ruthenium is undoubtedly the star metal in the present search for therapeutic agents. We collected nearly 250 papers on this topic in the time-span considered by this review, most of which are dedicated to the synthesis of new Ru(II) and Ru(III) complexes as potential anticancer drugs and to the elucidation of their mechanism(s) of action. Attention has also been paid to Ru compounds as antibiotics, antiviral, and antimalarial agents.

The history of ruthenium-based complexes as cisplatin contenders started in 1980, when its analogue chloro-ammine-Ru(III) compounds were found to have anticancer activity in rats. Their action was limited by poor solubility until four years later when a dmso-Ru(II) species, *cis*-[$RuCl_2(dmso)_4$], was shown to be active against both primary and metastatic cancers, although less effective than cisplatin, but with fewer side effects compared with the platinum drug. Activity against metastatic cancers is a feature shared by other Ru complexes, some of which have recently entered clinical trials.

In physiological solutions, ruthenium is stable in two oxidation states, Ru(II) and Ru(III), where the latter is considered to be less reactive. Both states can form six-coordinated octahedral species, which is a feature that facilitates finer tuning of the steric and electronic properties of the complex by intervening with the two "extra" axial ligands. The rate of ligand exchange in ruthenium complexes is comparable to that for platinum, i.e., a range of 10^{-2} to 10^{-3} s^{-1}, which is on the scale of an average cell's lifetime, thereby giving the molecules high kinetic stability and preventing rapid equilibration reactions. Thus, the complex remains intact on its way to the target and it also remains viable throughout its interaction with the cell. The fine-tuning of ligands can intervene in the kinetics of the complex to allow better control of its stability. Ligand tuning can also stabilize the Ru(II) oxidation state in the air to yield low-reactive species even when organometallic bonds are present.

Ru(III) complexes are considered to be pro-drugs due to their relative inertness compared with Ru(II) species. It is commonly thought that they should undergo "activation by reduction" to transform into the active drug, although some researchers dispute this opinion [129]. However, this mechanism appears to be possible, especially in solid tumor tissues where fast-growing cells with insufficient vascularization generate a hypoxic (reducing) state and lower the pH of the environment. Moreover, tumor cells often overexpress transferrin. Ruthenium is able to mimic iron during its interaction with this protein (as well as albumin), which it uses for transport and to achieve more selective entry into cancer tissues. The mechanisms that underlie the antineoplastic activity of ruthenium are more complex and less understood than those of platinum. Binding with DNA should be the main route, but a number of interactions that occur inside and outside the tumor cells are also emerging slowly [130].

The history of anticancer Ru chemistry shows clearly that three basic classes of active compounds have been obtained: Ru-dmso compounds (e.g., NAMI-A), Ru(III) complexes of the type [LH]*trans*-[$RuCl_4(L)_2$] (e.g., KP1019), and organometallic

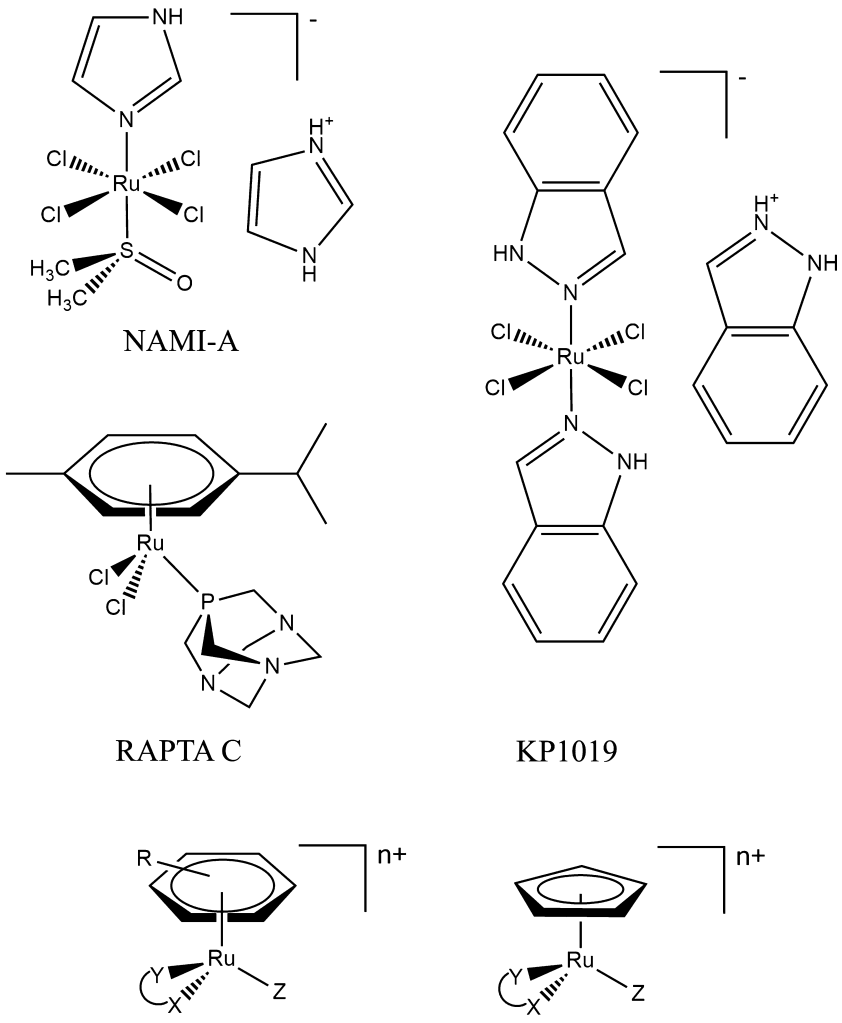


Fig. 4. Anticancer ruthenium complexes.

Ru(II)-arene complexes with the general formula of [(η^6-arene)Ru(en)Cl][PF_6] (e.g., RAPTA-C) (Fig. 4). These three groups of active compounds have different chemical and biological properties, and their in vivo anticancer activities also differ, where some are active against primary tumors, but others only against metastases. Some compounds are believed to interact with DNA, whereas this is questionable or unlikely for others (e.g., NAMI-A). Thus, there are no general guidelines for the synthesis of new active species [130].

4.1. Ruthenium-arene complexes

The long-lasting success of arene-ruthenium-based anticancer drugs is linked strictly to the amphiphilic properties of the arene-ruthenium system, where the hydrophobic arene ligand is flanked by the hydrophilic metal centre, as well as to the synthetic diversity of the arene moiety, which is an excellent scaffold for grafting organic segments to facilitate targeted chemotherapy [131,132]. The first observation of cytotoxic activity in a ruthenium-arene complex was reported in 1992, but the first prototypes of these complexes were only evaluated to assess their anticancer properties in 2001: (η^6-*p*-MeC_6H_4Pri)Ru(P-pta)Cl_2 (pta = 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane), designated as RAPTA-C by Dyson's group, as well as some analogues produced by Sadler. Although RAPTA-C only exhibits a low activity in vitro, it is highly active in vivo against metastatic tumors. Organometallic Ru(II)-arene compounds have been developed according to this strategy, including some containing phosphine, amine, and sulfoxide as co-ligands [9].

Recently, the use of intercalating ligands has been reported, including evidence of their effective DNA cleavage and activities, which are comparable to that of cisplatin in breast cancer [133]. In addition, heterocyclic ligands such as mercaptobenzothiazole and mercaptobenzoxazole were shown to be effective in half-sandwich arene–Ru complexes against several cancer cell lines, but remarkably not against healthy ones, where there was a non-intercalative interaction with DNA [134]. It was also demonstrated that substitution of the aromatic ring of the heterocycle, or the addition of a second hydrogen-bond donor on the heterocycle itself, reduced the cytotoxicity of the complex, thus a careful choice of ligand must be considered.

A good antitumor activity is obtained when the arene moiety is represented by the cyclopentadienyl ligand. The [Ru(II)(η^5-C_5H_5)(bipy)(PPh_3)]$^+$ species was described as a very promising large spectrum anticancer agent because it has a higher activity compared with cisplatin in a number of cancer cell lines, as well as in cisplatin-resistant tumors [135]. Similar results were obtained with analogous Ru(II) complexes where bipy was

substituted by *N*,*O* or *N*,*N*′ heteroaromatic ligands, such as 2-benzoylpyridine, 2-acetylpyridine, 1-isoquinolinyl phenyl ketone, and di(2-pyridyl)ketone, at concentrations in the nanomolar range [136].

However, the most widely used arene ligand is *para*-cymene, which is used in association with a wide range of N, S, and O donors, thus any attempt to order them into classes and discuss each thoroughly would result in a review within this review. Thus, we only mention a few of these coligands to illustrate their effective antiproliferative or cytotoxic activities, including conjugated biological molecules or biologically active species (peptides, antibiotic glycosides, flavones, curcumin, and steroids) [137–142], TSCs [143,144], am(m)ines [145,146], and heterocycles [134].

4.2. Polypyridyl–Ru(II) complexes

Polypyridines are multidentate ligands such as bipyridines, 1,10-phenanthrolines, and terpyridines, which are able to confer photoluminescent properties on metal complexes, such as Ru(II) species, via a metal-to-ligand charge transfer. Polypirydines are also flat heteroaromatic compounds with intercalating activities, which explains why their complexes have been tested as antitumor drugs. Thus, Ru(II) polypyridyl complexes have emerged as promising DNA structure probes and as anticancer agents due to their unique photophysical and cytotoxic properties [147]. Polypyridine ligands are often associated with other donor molecules. Their complexes exhibit anticancer activities [148] and they have been investigated thoroughly to elucidate their mechanisms of action [149–153], although polypyridyl–Ru(II) species have been studied in most cases in terms of their photocleavage reactions due to their specific properties. For example, a Ru(II)-polypyridyl complex has been grafted onto nanoparticles, such as mesoporous silica, for delivery to the target cells, as well as being cleaved by visible light to allow release into the cellular medium as an active aquo species, with promising results [154]. Intercalation seems to be the most likely mechanism that allows this type of complex to be active against tumor cells [155–158], although in some cases it has been demonstrated that they operate via DNA photobinding [159] and photocleavage [160,161], or they can also induce cancer cell apoptosis by acting on mitochondrial pathways [162,163].

4.3. Ruthenium complexes with thiosemicarbazones

Like the other noble metals mentioned earlier, ruthenium complexes with TSCs have been synthesized extensively and studied as therapeutic agents, since Beckford et al. reported (in 2009) the first structurally characterized ruthenium-arene half-sandwich complexes containing both the {(η^6-*p*-cymene)Ru(II)} moiety and 9-anthracenyl-thiosemicarbazone derivatives as ligands [164]. Subsequently, polycyclic aromatic TSCs have been employed often in Ru(II) compounds [165].

TSC-containing complexes generally exhibit good cytotoxicity against different human cancer cell lines and their biological activities appear to be modulated by the TSC moiety. Their electronic, steric, and functional properties have been tuned in different ways, especially by the careful choice of the coligands (ranging from arenes [143,144,166] to phosphines and arsines [167–169]), and the results obtained are rather encouraging, although their distinct mechanisms of action and biological targets still need to be elucidated.

4.4. Mitochondria targeting

A recent new approach to cancer treatment involves the exploitation of mitochondrial disruption mechanisms, which circumvent the upstream apoptotic pathways that can be mutated or that are simply lacking in tumor cells. In fact, the mitochondria in neoplastic tissues are functionally and structurally different from those in healthy ones, i.e., cancer cells have higher mitochondrial membrane potentials, which make them more vulnerable to mitochondrial perturbation than normal cells. From this perspective, many mitochondria-targeting agents have been designed to disrupt their normal potential, to further permeabilize their outer membrane, to release proapoptotic proteins, and to knock out the mitochondrial functions, thereby activating the cell death machinery.

Some ruthenium polypyridyl complexes have been shown to induce apoptosis via mitochondrial pathways, where the loss of the mitochondrial membrane potential [170] is accompanied by a release of cytochrome *c* [171], or an increase in the levels of reactive oxygen species [162,172–174], and this mechanism is similar to that found with completely different Ru(II) complexes based on arene–carboline ligands [175] or the methylimidazole-phenanthroline system [176]. Lipophilic ruthenium complexes can selectively accumulate in mitochondria [177,178], thereby inducing cell death via programmed mitochondrial death.

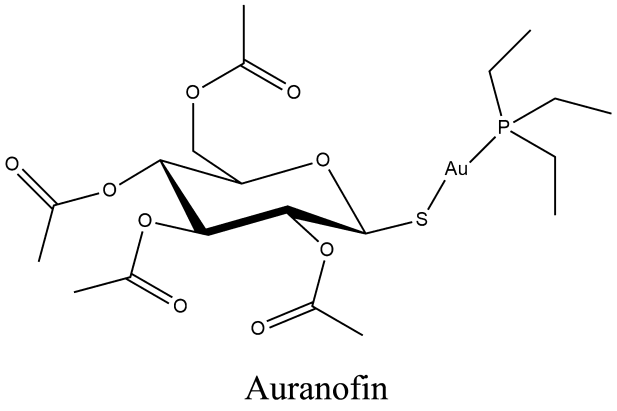
4.5. Different activities

Ruthenium complexes are very important in new antibacterial and antiparasitic drugs due to their high efficacy. At present, the most widely studied complexes are ruthenium octahedral species with Schiff bases, followed by complexes with planar ligands and an overall flattened geometry, which are suitable for DNA intercalation. The presence of the 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1] decane (PTA) ligand is often advisable to obtain higher solubility in water. Another strategy involves synthesizing complexes that mimic active organic drugs [179].

Recently reported Ru(II) species with antibacterial activities include mixed polypyridyl (2,2′-bipyridyl) complexes with *N*-phenyl-substituted diazafluorenes, which were prepared for testing against methicillin-resistant *S. aureus*, thereby yielding significant improvements in both the minimum inhibitory concentration and the minimum bactericidal concentration compared with methicillin (used as the positive control). These complexes possess much stronger antibacterial effects than the ligands alone. Their biological safety when tested on normal human skin keratinocytes may allow their use in the formulation of topical antibiotics [180]. Dinuclear Ru(II) 1,10-phenanthroline complexes were assessed against *S. aureus*, methicillin-resistant *S. aureus*, *E. coli*, and *P. aeruginosa* with remarkable results, where they could kill these bacteria within 2–6 h [181]. In general, Ru(II) polypyridyl complexes are effective against different bacterial strains and, as expected, their antimicrobial activity is correlated with DNA binding in the intercalative mode, although molecular docking studies also support DNA interactions with complexes via hydrogen bonds and van der Waals interactions [182].

Ru(II) compounds were also shown to be effective in the treatment of *M. tuberculosis* when phosphine/diimine/picolinate complexes were tested. They had up to 150 times higher activities against the bacterium compared with the free ligands and they performed better than rifampin, with low cytotoxicity and high selectivity [183,184].

The anti-parasite properties of Ru(II) complexes have been demonstrated against a number of microorganisms. In the case of *Leishmania*, Ru(II)-tetramine nitrosyl complexes exhibited 98% inhibition of parasite growth [185], while organometallic ruthenium-arene-ketoconazole (KTZ) complexes markedly enhanced the activity against promastigotes and the intracellular amastigotes of *Leishmania major* compared with free KTZ, or with similar ruthenium compounds that did not contain KTZ. Their selectivity was also remarkable, with a clear preference for



Auranofin

Fig. 5. The Au(I)-based arthritis treatment auranofin.

the *Leishmania* parasites compared with human fibroblasts and osteoblasts, or murine macrophages [186]. Organoruthenium(II) complexes with TSCs were found to be active against two trypanosomes, *T. cruzi* and *T. brucei* [187], and *Trichomonas vaginalis* [188]. Finally, η^6-areneruthenium(II) phosphite complexes, which are highly cytotoxic, have been applied in the treatment of alveolar echinococcosis [189].

5. Gold

Gold was one of the first metals used as a treatment for diseases thousands of years ago, but its exploitation in modern medicine was mainly restricted to the cure of rheumatoid arthritis since the mid-1930s, starting with prototypal Au(I) thiolates and ending with auranofin (Fig. 5), an Au(I) thiolate-triethylphosphine complex. Since the introduction of the latter in 1985, no other gold compound has been admitted to clinical use for rheumatoid arthritis or any other disease. Although this complex (like most of its analogues) has a certain degree of toxicity, it exhibits an in vitro anticancer activity that is similar to that of cisplatin. Indeed, a series of analogue Au(I) complexes were synthesized, which were found to have strong cytotoxicity against hemolymphatic cancers. Improvements were made using diphosphine ligands, but these complexes did not enter clinical trials due to their high cardiotoxicity.

By contrast, the class of Au(III) compounds appears to be a good source for an alternative to cisplatin because Au(III) has the same d^8 electronic configuration as Pt(II) and it forms square planar tetracoordinated complexes, which should interact with DNA in a similar manner, at least hypothetically. Moreover, the ligand exchange kinetics are relatively slow in both cases, although they are slightly faster in Au(III) complexes. Unfortunately, their relatively poor chemical stability in solution slowed down improvements until the introduction of stabilizing ligands in the mid-1990s. These ligands, such as those based on nitrogen donor groups, provide sufficient stability in physiologically relevant conditions. A series of square planar Au(III) complexes with anticancer activities has been reported, but their mechanism of action is far from being understood because the evidence is contradictory depending on the complexes examined. Apart from their structural similarities, however, it is clear that Au(III) compounds do not act in the same manner as cisplatin in the path leading to apoptosis. Interactions with DNA have been demonstrated for some complexes, especially those with flat polyaromatic ligands, such as terpyridine. They interact with DNA in the intercalative mode, but other cases of in vitro interactions with DNA strands appear to be rather weak. In addition, effective bonds with serum proteins were detected, mostly with sulfur-containing proteins such as GSH and thioredoxin reductase, or with albumin. Some Au(III) dithiocarbamate complexes significantly inhibit the tumor growth of MDA-MB-231 in breast tumor-bearing mice, which is associated with proteasome inhibition and massive apoptosis induction [190].

Au(III) complexes also share a wide range of side-effects with cisplatin: high toxicity, induced drug resistance, poor cancer-cell specificity, and limited bioavailability. These features have hindered rapid progress in the field of Au(III) compounds as therapeutic agents. However, a number of gold complexes have been shown to be excellent candidates in the search for cisplatin successors, based on the use of rational design to create very effective, non-toxic, and potentially selective gold-based drugs with the aim of site-specific delivery in localized cancer, especially for complexes based on sulfur donors such as dithiocarbamates [191]. In this section, we provide a survey of the advances in this area during the last four years.

5.1. Dithiocarbamate complexes with Au(I) and Au(III)

As mentioned earlier, these types of ligands can reduce the systemic and renal toxicity of metal compounds used in cancer treatments. Au(III) species with dithiocarbamate ligands also have outstanding in vitro and in vivo antitumor properties [191–193], while Au(I) phosphino-dithiocarbamate complexes are effective against a number of cancers, where their efficacy depends on the nature of the phosphine ligand. In particular, triphenylphosphine yields more stable species with high cytotoxicity, while 1,6-bis(diphenylphosphino)hexane increases the selectivity for HeLa cancer cells [194,195]. Another strategy employed in the design of effective drugs is to prepare dithiocarbamate Au(III) complexes that contain oligopeptides to exploit their peptidomimetic properties, thereby allowing their selective transport inside cancer cells. This strategy has obtained good results with triple-negative breast cancer [196] and other cancer cell lines [197].

5.2. Phosphine and phosphine-derivatives Au(I) complexes

Gold-phosphine compounds were investigated after the antiarthritic drug auranofin (thiolate–Au-PEt_3 complex) was found to have biological activity against different cancer cells. A series of auranofin analogues containing thiolate ligands were prepared, as well as bis(phosphine)Au(I), phosphine–gold-halides, and phosphine-gold-alkynyl complexes. Their mechanism of action appears to be connected mainly to the inhibition of thioredoxin reductase [198]. Au(I) phosphino complexes with a sugar derivative were active against glioblastoma in human and mouse cellular lines, and they were well tolerated by rats [199]. A series of aminophosphine-thiolate Au(I) complexes exhibited high cytotoxicity in human cell lines of cervical and breast cancers, thereby demonstrating the potent inhibition of thioredoxin reductase, whereas the interaction with DNA had no significant influence on its structure [200].

Solubility is always an issue for drug administration, which is a limit that many potential anticancer metal complexes have to overcome. A soluble diphosphine Au(I) complex, bis-phosphinoquinoxaline–Au(I) chloride was reported to have low toxicity and high anticancer potential at a concentration of 0.5 μM in a sarcoma cell line, and it was well tolerated in animal models. It was demonstrated that this complex specifically inhibits the enzymatic activity of thioredoxin reductase by binding to selenocysteine residues [201], but without targeting other well-known selenol and thiol groups found in biomolecules [202].

Flanking the phosphine with an appropriate coligand yields active complexes, as found with azolate species such as pyrazolates and imidazolates, which are substituted with deactivating groups, including trifluoromethyl, nitro, or chloride moieties. These substituents can increase the solubility of the complex in

water and other polar media. This design strategy led to the synthesis of gold(I) compounds with antiproliferative effects up to 70 times higher than cisplatin [203]. In addition, the presence of a polar moiety on the phosphine ligand may yield active and soluble Au(I) compounds. Sodium triphenylphosphane monosulfonate, sodium triphenylphosphane trisulfonate, 1,3,5-triaza-7-phosphaadamantane, and 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane were associated with a thiolate ligand to yield potent antiproliferative complexes against a human ovarian carcinoma cell line (A2780/S) and its cisplatin-resistant variant (A2780/R), which depended strictly on the types of thiolate and phosphane ligands [204]. In the same manner, diphosphines bearing imidazole or thiazole substituents yielded water-soluble Au(I) complexes, which were tested against three human cancer cell lines and a rat hepatoma cell line, where their apoptotic activity was correlated with the lipophilicity of the compounds [205].

The cytotoxic activity of diphosphine-containing Au(I) complexes is related strictly to the substituents on the phosphorus atom, with the highest for the phenyl group and the lowest for the methyl group, as noted previously, but also to the length of the linker connecting the two phosphorus atoms (highest with five or six carbon atoms). Thus, both the steric and electronic properties appear to be important in the design of effective gold complexes [206].

5.3. Organometallic complexes of Au(I) and Au(III)

The presence of a direct metal-carbon bond in Au(I) and Au(III) complexes appears to be rather beneficial for their stability and speciation in aqueous solutions, thereby leading to a vast panel of compounds with remarkable anticancer activities [207], including cyclometallated Au(III) species, gold alkynyl complexes, and gold *N*-heterocyclic (NHC) carbene compounds. In particular, the latter have been reported extensively in the most recent studies and, together with phosphine derivatives, they represent the most widely studied class of gold-based potential antitumor drugs. These complexes have been reviewed thoroughly in the past year [207–209] so we direct the reader to the appropriate reports.

5.4. Different activities

Gold nanoparticles (nanoshells/nanocages) are emerging as efficient carriers in targeted drug delivery systems [210]. This approach may apply to cancer treatment [211,212] as well as improved vaccine presentation by dendritic cells [213]. A series of different gold-based nanomaterials has been reported recently for these purposes.

In addition, Au(I) and Au(III) complexes have performed remarkably well in the treatment of leishmaniasis, malaria, and tuberculosis, and they have also been tested against HIV infection. The anti-inflammatory properties of new Au(I) complexes are still being evaluated for the treatment of rheumatoid arthritis [214].

The recently proposed anti-leishmanial drugs are based on Au(I) and Au(III) complexes of benzimidazole derivatives [215]. Free benzimidazoles were completely ineffective, but their gold complexes exhibited good activities against *Leishmania* protozoa and high selectivity, where Au(I) compounds were almost 50 times more toxic to the parasite than macrophages. Auranofin was also found to be effective against this cutaneous disease [216].

The activity of gold complexes against *Leishmania* parasites may be linked to the inhibition of trypanothione reductase, as suggested in a recent study [217]. Trypanothione is an unusual form of GSH that contains two molecules of GSH joined by a spermidine (polyamine) linker, which is found in parasitic protozoa such as *Leishmania* and trypanosomes, where its main function is defense against oxidative stress, thus the impairment of this reduction enzyme may severely damage the protozoan.

Recent antimalarial agents based on gold complexes include Au(I) phosphine complexes containing thiosemicarbazonato ligands [218], *N*-heterocyclic ylideneamine gold(I) complexes [219], and gold(I) TSC species where the ligand is tetrahydrothiophene [220]. Their mechanism of action appears to be connected to inhibition of the parasite cysteine protease falcipain-2, and a recent attempt to verify this hypothesis demonstrated that gold complexes are actually able to inhibit this enzyme. Nevertheless, these studies were not able to establish any direct correlation between enzyme inhibition and reduced *P. falciparum* growth, thereby suggesting that falcipain-2 inhibition represents just one of the various mechanisms that allow gold compounds to effectively antagonize *P. falciparum* replication [221]. Finally, gold compounds were tested against HIV infection, with interesting preliminary results given the incredible complexity of this disease. The compounds evaluated in these studies were based on complexes such as Au(III) tetrachlorides [222], which are able to inhibit the integrase enzymatic activity, probably via protein oxidation. By contrast, bis(thiosemicarbazonate) Au(III) complexes inhibit HIV replication at cytostatic concentrations [223].

6. Silver

At present, silver has no known biological role in the human body, whereas it has a well-recognized toxic effect on lower organisms.

It is known that most bacteria are affected adversely by silver. Those that are not killed can neutralize it by depositing the undesirable metal in specialized tiny cavities localized in the cell wall; indeed, *P. stutzeri* was isolated in a silver mine.

Some of its salts, such as silver nitrate, have been used since the mediaeval age until the early twentieth century as remedies for itchiness and warts. Since the 1880s, silver nitrate solution eye drops have been used to prevent forms of blindness that we now know are caused by microbial infections.

The reputation of silver in the medical field has extended to the present; in fact, its medical properties as an antibacterial, antiseptic, and anti-inflammatory agent are now well recognized and the synthesis and activity of silver complexes have been reported widely [224–226]. However, the number and variety of ligands and co-ligands employed in this task is so vast that any attempt to group them into classes is beyond the scope of this review [227].

For example, the properties of silver as an anti-inflammatory agent have been histologically recognized for burn wounds [228] and the US Food and Drug Administration (FDA) approved the use of Ag(I) sulphadiazine compounds with well-established and potent antibacterial actions against burn injuries [226,229]. Di- and polynuclear Ag(I) saccharinate complexes with tertiary monophosphanes may be active against bacteria such as *S. aureus* and *Salmonella typhimurium*, where their MIC values were higher than those found for silver nitrate and Ag sulphadiazine, which were used as controls.

Among the Ag(I) saccharinate complexes, $[Ag_2(sac)_2(\mu\text{-}dppm)H_2O]\cdot H_2O$ (where sac is saccharinate and dppm is 1,1-bis(diphenylphosphino)methane) was shown to have a very high antibacterial activity against standard bacterial strains such as *S. aureus*, *E. coli* and *S. typhimurium*, and its activity was much higher than that of silver nitrate and silver sulfadiazine, as well as other well-known broad-spectrum antibitiotics such as ciprofloxacin and gentamicin [230].

The inhibition of cell growth by Ag(I) saccharinate complexes may be associated strictly with their binding affinity for the DNA molecule [231]. Furthermore, Ag^+ ions can kill bacteria and destroy

viruses, but they are also able to kill antibiotic-resistant bacteria, which could be more important for modern medicine.

For example, complexes of Ag(I) with phosphate derivatives of pyridine and benzimidazole were shown to be active against *Candida albicans* strains (with MIC values of ~19 μM). In particular, $[Ag(2\text{-bimOpe})_2]NO_3$ (where 2-bimOpe is 1*H*-benzimidazol-2-ylmethyl diethyl phosphate) was highly active against *P. aeruginosa* and methicillin-resistant *S. epidermidis*, with MIC values of about 5 and 10 μM, respectively, whereas the free ligands had no activity [232].

In addition, silver complexes have been tested to assess their anticancer performance. For example, Ag(I) saccharinate complexes exhibit high cytotoxicity against human lung carcinoma and human breast adenocarcinoma cell lines in addition to their antibacterial and anti-inflammatory activities [230].

An interesting complex, the Ag(I) tartaric acid chelate named aliargentumycine (AAgM), exhibited cytotoxicity against hematopoietic tumors, which was comparable to that of cisplatin. Its antineoplastic activity was studied in T-47D (solid human breast ductal carcinoma) and Jurkat (disseminated T-cell acute lymphoblastic leukemia) cell lines. Quantitative pharmacodynamic and kinetic models were used to study the behavior of the AAgM complex, which detected a noticeably improved cytotoxic activity, and it was higher than that of cisplatin. Indeed, cisplatin exhibited no cytotoxicity against T-47D cells at <122 ng/ml, whereas AAgM exhibited cytotoxicity at 1.9 to 30.5 ng/ml. The specific mechanism of action was investigated using a common assay (TUNEL test) employed for detecting DNA breakup, which showed that the antineoplastic action of AAgM is mediated by apoptotic signaling cascades (apoptosis). In addition, the activity was strongly correlated with the specific structure of the complex, which comprises a polymeric hydrate sequence with distorted trigonal bipyramidal geometry around Ag^+ ions. Due to the presence of hydrophilic and lipophilic moieties, the AAgM complex is soluble in aqueous and lipid media, which makes it particularly suitable for the treatment of particular types of tumors, especially the solid neoplasms that result from epithelial and mesenchymal cells [233].

An interesting recent review highlighted the antineoplastic activities of several Ag(I) complexes against different types of tumors and the anti-proliferative actions of the complexes were summarized [234]. The coordination numbers and stability of the complexes were considered, but there were no clear correlations among them and the biological activities of these compounds.

It has been reported that Ag(I) complexes of ligands with different donor atoms, such as oxygen from carboxylic acids or nitrogen, or oxygen from amino acids or phosphorous donor ligands, exhibited significant in vitro and selective anti-proliferative actions compared with the activity of cisplatin, thereby showing that the activities of the Ag(I) complexes were comparable or higher than that observed for cisplatin in some cases. This feature was also demonstrated for compounds synthesized and tested in previous years. For example, the Ag(I)6- (or 7- or 8-)hydroxycoumarin-3-carboxylato complex exhibited a stronger activity than cisplatin against Hep-G2 cells (hepatocellular carcinoma) [235].

It has been reported that the hydroxyl group, especially in the sixth position, is particularly important for the mechanism of action.

$[Ag(tpp)_3(asp)](dmf)$, $[Ag(tpp)_3(o\text{-Hbza})]$ and $[Ag(tpp)_3(p\text{-Hbza})]$ mixed ligand complexes, where tpp = triphenylphosphine, aspH = *o*-acetylsalicylic, *o*-HbzaH = *o*-hydroxy-benzoic acid, and *p*-HbzaH = *p*-hydroxy-benzoic acid, were also more active than cisplatin. In particular, $[Ag(tpp)_3(p\text{-Hbza})]$ exhibited a significantly higher in vitro activity than cisplatin against LMS (leiomyosarcoma) and MCF-7 (human breast adenocarcinoma) [225].

The binding constant of DNA with the Ag-complexes was 2–5 times higher than the analogous value with cisplatin. The compound with the *p*-HbzaH ligand was much more active and it could form hydrogen bonds with the DNA bases, thereby strengthening the interaction between DNA and the Ag complex, yielding a more stable DNA–Ag complex.

Ag(I) heterocyclic carbene complexes, which are known for their antimicrobial activity, have been tested using a panel of clinical strains of bacteria and fungi, which are responsible for many skin, soft tissue, respiratory, wound, blood, and nosocomial infections, and very promising results were obtained, even with resistant bacteria. They have also been examined in recent years with several cancerous cell lines [236]. Indeed, *N*-heterocyclic carbene (NHC) benzyl-substituted-silver acetate complexes exhibited cytotoxicity that was three times higher than cisplatin when tested in vitro on the human renal cancer cell line Caki-1 [237]. Furthermore, it has been reported that they exhibited higher activity against cancerous breast cells than cisplatin itself when the 4,5-dichloroimidazolydene ligand was present. Subsequently, a new class of Ag(I) carbene complexes was studied to assess their antitumor activity, and their mechanism of action at the cellular level was examined, where the results discussed were compared for Ag, but also for Au, Pt, Pd, Cu, Ni, and Ru complexes, containing NHC ligands as antitumor agents [238,209]. Ag(I) complexes often exhibit higher activities compared with the free ligands. For example, bis-benzimidazolium salts are normally inactive, but they enhance the anticancer action after binding with Ag(I) ions in complexes such as 3,3′-[1,2-phenylenebis(methylene)]bis (1-ipropyl-benzimidazolium) disilver (I) bis (hexaflourophosphate) or 3,3′-[1,4-phenylenebis (methylene)] bis(1-ipropyl-benzimidazolium) disilver(I) bis(hexaflourophosphate), and a dose-dependent anti-proliferative activity was detected against the HCT 116 human colorectal cancer cell line. This demonstrates that silver ions have an important function in the death of cancer cells. In addition, their cytotoxicity appears to be dependent on the substituents on the ligand. The length of the *N*-alkyl chain might influence the activity of these complexes by affecting their lipophilicity. Indeed, the anti-proliferative activity is influenced by the lipophilicity of the complexes by improving the uptake of silver inside cells, where it may hinder cellular respiration and cellular metabolism [239]. Finally, five novel Ag(I) complexes with mixed ligands, tris(pyrazol-1-yl)methanesulfonate (Tpms), triphenylphosphane (PPh_3), tricyclohexylphosphane (PCy_3), and 1,3,5-triaza-7-phosphaadamantane (PTA), i.e., [Ag(Tpms)], $[Ag(Tpms)(PPh_3)]$, $[Ag(Tpms)(PCy_3)]$, $[Ag(PTA)][BF_4]$, and [Ag(Tpms)(PTA)], had efficient activities against several bacteria and fungi, thereby indicating their potential as antiseptic drugs, as well as potent antiproliferative activities against human malignant melanoma (A375), which was much higher than that of silver nitrate [240]. Among the most interesting new results are those regarding a new generation of silver agents, including their nanoparticle (NP) formulations. NPs have large surface/volume ratios, which can improve their potential activity in the treatment of multi-drug-resistant bacteria, and they are becoming a new therapeutic tool to combat bacterial resistance. Therefore, different NPs have been synthesized in order to increase the permanence time of silver at the site of infection, e.g., silver carbene complexes (SCCs) inside the lung. For example, the use of Ag-(SCK) NPs (SCK = shell crosslinked) was especially beneficial in lungs that were chronically infected by cystic fibrosis [241]. SCK NPs have been proposed for capturing and protecting silver and the in vitro antimicrobial activity of silver-loaded SCKs was tested against *P. aeruginosa.* Furthermore, Ag-NPs had a potent activity toward ocular pathogenic filamentous fungi compared with natamycin, a polyene macrolide antifungal drug used for topical ophthalmic administration [242]. It seems that the use of silver NPs can be very useful in fighting infections by allowing the drug to reach the infected locations at higher doses, thereby overcoming resistance. In addition, this

could reduce the dosage and minimize the possible toxicity. For example, a NP complex containing silver sulfadiazine (AgSD), which was prepared using a poly(amido amine) (PAMAM) dendrimer with SD and silver, exhibited enhanced solubility and an improved antibacterial activity, and it has recently been applied in a topical cream formulation for the cure of infections due to burns [243]. AgNPs combined with doxorubicin (DOX) have been tested against human breast cancer cell lines T47D and MCF7. They produced conformational changes in DNA via electrostatic and intercalative interactions. The mixture greatly reduced the proliferation of the tested cells compared with the Ag NPs alone or DOX alone [244]. In addition, silver NPs have been tested to assess their antiviral activity. Recently, it was demonstrated that they can inhibit HIV-1 infection in human cervical tissue organ culture [245].

Many other novel complexes have been synthesized and tested to assess their antibacterial activity and their anticancer potential, but we have summarized the most novel and interesting results among the huge number of silver complexes with proven potential uses in medicine.

Given their low toxicity in humans, they may have important roles in the treatment of diseases and they could provide starting points for the design of future silver drugs to combat antibiotic-resistant bacteria as well as different types of cancer. Thus, silver has a valuable role in modern clinical medicine and there is great interest in the continuous development of its novel compounds.

7. Copper

Among all the noble metals, copper is the only essential one and it participates in a number of biological processes, thus its homeostasis is strictly regulated.

Copper complexes have been investigated for many therapeutic purposes, such as antimalarial, antifungal, and antibacterial agents, in the treatment of Alzheimer's disease due to its neuroprotective action, and recently as potential drugs to combat Parkinson's disease, amyotrophic lateral sclerosis, diabetes, inflammatory states (i.e., rheumatoid arthritis), skin wounds, cardiovascular diseases, and leishmaniasis. Much research has been performed, especially in terms of their action as anticancer agents, although the their mode of action is not yet fully understood and it merits more attention. Nevertheless, one well-supported hypothesis is based on the intracellular formation of reactive oxygen species (ROS) via the thiol-mediated reduction of Cu(II) to Cu(I), and further support has come from the most recent studies [246]. DNA cleavage has also been demonstrated in some studies, especially for polypyridines and polyphenols [247].

Recent studies of copper complexes as therapeutic agents were reviewed by Duncan and White in 2012 [248], thus we focus on the latest results and the complexes that were not examined in their study in terms of both Cu(II) and Cu(I) oxidation states.

7.1. Thiosemicarbazone Cu(II) complexes

As discussed in the previous sections, TSCs have essential roles in the synthesis of potential anticancer agents, including those based on copper complexes [249]. These derivatives are active in liver cancer when the TSC bears halogen substituents [250], in different colon cancer lines when the TSC is based on the piperonal structure [251] or a bis(thoisemicarbazone) copper complex is formed [252], or when conjugated to D-proline where the L-enantiomer is less effective [253]. Their mechanism of action is not attributable to DNA binding and it is still under study.

7.2. Polynuclear copper complexes

Cu(II) di- and trinuclear complexes have remarkable cytotoxic activities and antiangiogenic properties [254], generally via ROS formation pathways. In addition, a trimetallic species containing μ-oxamido-bridges was active against liver and lung cancers, but via DNA binding and intercalation [255]. The same results have been reported for another trinuclear complex containing a disubstituted terpyridine, where the authors demonstrated that this complex could bind and break the DNA strands with high efficiency, and the cleavage activity depended on the number of copper atoms present in the complex, which decreased in the order: 3 > 2 > 1. This trimetallic species was very active against leukemia, with a strong propensity to enter the cell and localize to the nucleus [256]. Thus, polypyridyl ligands can also confer high cytotoxicity on Cu(II) polynuclear species, but their mechanism of action may be different according to the type of ligand used. Indeed, a dimetallic 1,10-penanthroline complex was highly active against cisplatin-resistant ovarian cancer at a nanomolar concentration, but the mechanism involved oxidation of the DNA duplex via ROS formation in this case [257]. After changing the ligand structure completely, salen or salophen Cu(II) dinuclear complexes exhibited a propensity to bind and cleave DNA, which suggests that this could be a possible mode of action for these types of complexes [258].

It is interesting to note that polynuclear Cu(I) complexes also exhibited potential anticancer activities, where the ligands used were cyclodiphosphazane and pyridyl types. Some of these species were more active than cisplatin against different cancer cell lines by damaging DNA, blocking the cells in the G1 phase of the cell cycle, and inducing apoptosis via a p53-dependent pathway [259].

7.3. Copper complexes with polypyridyl ligands

As reported earlier, polypyridines (bipyridines, terpyridines, phenanthrolines, etc.) comprise a class of ligands that have been employed widely in the synthesis of metal complexes for therapeutic uses because they can interact with DNA via intercalation and they are very effective in cancer treatments. In the case of copper, these complexes have been tested to assess their cytotoxicity with interesting results, where those with 1,10-phenanthrolines exhibited the most promising anticancer activities, thus they are discussed in a dedicated section.

A full series of polypyridines were flanked by a quinolinato ligand to yield Cu(II) species that were all active against human hosteosarcoma and breast carcinoma at low micromolar doses. A DNA cleavage mechanism was demonstrated for these complexes in addition to their superoxide dismutase (SOD) mimicking activity, and the possibility of effective binding with sulfur-containing biomolecules, such as cysteine and reduced GSH [260,261]. An analogous study was undertaken where different polypyridines were associated with a phenolate ligand, which showed that the cytotoxic activity was higher than cisplatin in breast and cervical cancer, and the DNA cleavage ability was effective at micromolar concentrations [262]. Furthermore, Cu(II) complexes of terpyridine derivatives exhibited good cytotoxicity against lung adenocarcinoma [263,264] and breast cancer cell lines, but low toxicity to normal cells [265]. The most active derivative was an anthracenyl-terpy, which obtained remarkable results against a wide range of cancer lines [266]. Their mechanism of action is based on DNA intercalation and cleavage. Finally, bipy Cu(II) complexes with glycine were active against breast and liver cancer, where they also

inhibited the growth of different pathological bacteria and fungi [267].

7.4. Copper complexes with phenanthrolines

Copper–phenanthroline complexes are known to oxidatively damage and cleave nucleic acids by acting as nucleases [268,269]. Recently, it was demonstrated that 1,10-phenanthroline can enhance copper complex entry into tumor cells and induce apoptosis by inhibiting the proteasome activity, thus its ternary complexes may be good potential anticancer drugs [270]. Subsequently, Casiopeinas® [271], a mixture of ternary Cu(II) complexes with different 1,10-phenanthrolines or bipyridines together with an amino acid ligand, exhibited cytostatic, cytotoxic, and antineoplastic activities with promising results as clinical antitumor drugs. Recently, their mechanism of action was studied [272], which showed that they induce oxidative stress and mitochondrial dysfunctions [273], as well as DNA fragmentation and base oxidation, thereby suggesting that their action may be attributed to ROS generation after copper reduction [274]. In general, ternary 1,10-phenanthroline copper complexes have been investigated widely as chemotherapeutics by testing different co-ligands to optimize their activity and to reduce their toxicity, and by trying to elucidate their modes of action. Good results have been obtained with oxazolidin-carboxylates against a vast range of cancer lines, where the activities were higher than that of cisplatin and there was some degree of selectivity [275], while *N,N′*-substituted-imidazolidine-2-thione was effective in the 1–3 μM range against both leukemia and carcinomas [276]. Furthermore, a dimetallic complex with terephthalate appeared to be a potent oxidative DNA cleaver with ROS production at a nanomolar concentration [257], which was active against cisplatin-resistant cancer lines. DNA cleavage may also be induced by UV light, as is the case with two tetracycline complexes (already reported as some of the most potent DNA cleavers) [277,278] of a ferrocene-conjugated tryptophan compound [279], or of a naphthalene-sulfonamide [280]. This topic should be investigated further because photocleavage can be a very useful tool in cancer treatment, as shown for ruthenium complexes.

7.5. Different activities

Like silver, copper has high activity against bacteria, viruses, yeasts, and fungi, both in its metal state and as coordination complexes. Copper vessels were used by the Egyptians to store water and to keep it uncontaminated and fresh for long periods, which is a tradition that was maintained by modern Indians because Ayurveda recommends this practice. Several recent studies have suggested the possibility of using this metal to control bacteria in situations where their proliferation should be inhibited. Thus, the use of copper wares to store drinking water could be a valuable aid to populations living in rural areas of undeveloped countries where a potabilization plant would be unaffordable. It was demonstrated that contaminated water kept in copper pots for 16 h eliminated the overall bacterial load of important diarrheagenic bacteria, including *Vibrio cholerae*, *Shigella flexneri*, enterotoxigenic *E. coli*, enteropathogenic *E. coli*, *Salmonella enterica typhi*, and *Salmonella paratyphi*. This was highly effective and any attempt to revive these bacteria failed, even after culture in enrichment broth, followed by plating on selective media [281]. Copper nanofilms were effective in inhibiting the growth of a number of nosocomial bacteria and *Enterobacter* species, thereby suggesting their possible use in touch surfaces in hospitals and healthcare settings, where germ proliferation and resistance are becoming serious issues [282–284]. This effect is called “contact killing” and it led to the approval of metallic copper as the first solid antimicrobial material by the US Environmental Protection Agency. Nevertheless, a thorough study of its ability to induce bacterial resistance has never been produced and it is advisable.

Copper and copper compound (Cu_2O, CuO, CuI [285]) NPs appear to be equally effective in microorganism control and their mechanism of action probably includes multiple toxic effects, such as ROS generation, lipid peroxidation, protein oxidation, and DNA degradation. A recent study in this area focused mainly on the cheap, safe, and efficient synthesis of such nanomaterials, as well as high stability and antibacterial activity. For example, the hydrothermal production of Cu, Cu_2O, and Cu/Cu_2O NPs have been performed in the presence of biocompatible surfactants such as polyoxyethylene, sorbitan laurate, and polyethylene glycol 8000 with different reaction times, which obtained particles of different sizes and compositions. Cu_2O NPs were most effective against *Bacillus cereus* and *Bacillus subtilis* [286].

Green synthesis of CuO NPs was performed using gum karaya as a biotemplate via a colloid-thermal synthetic process, which started from $CuCl_2{\cdot}2H_2O$ at different concentrations with heating at 75 °C and at 250 rpm for 1 h in an orbital shaker. The size of the CuO NPs depended on the concentration of the copper precursor where those with smaller dimensions (4.8 ± 1.6 nm) were highly stable, and they had significant antibacterial effects on both Gram classes of bacteria compared with the larger NPs (7.8 ± 2.3 nm) [287].

Factors such as agglomeration and the rapid oxidation of metallic Cu NPs may make their use rather difficult, thus a method for stabilization is often needed. They can be synthesized in the presence of a chitosan stabilizer by chemical means [288] or by loading them onto natural montmorillonite after reduction with a copper ammonium ion [289], which facilitates their stabilization over a three-month period. Another strategy utilizes poly-L-lysine-modified reduced graphene oxide as the carrier for the Cu NPs, which results in long-term stability and the hybrid material has an antibacterial effect, as well as excellent water solubility to support potential applications in microbial control [290]. Finally, a simple and effective method for synthesizing Cu NPs was achieved by reducing $CuCl_2$ in the presence of gelatin as a stabilizer, but without the need for strict conditions such as working in an inert atmosphere [291]. The particles obtained had a much higher activity against *E. coli* compared with those reported previously, and similar efficacy against Gram-positive *B. subtilis* and *S. aureus*.

Copper complexes elicit antimicrobial responses in both their Cu(I) and Cu(II) oxidation states, where the latter is the most representative of the types reported previously. Normally, they bear mixed ligands, where phenanthrolines are often associated with amino acids, [292–295] and other polypyridyl ligands [296], as well as antibiotic molecules, to enhance the activity of the drug itself. The association between 1,10-phenanthroline and antibiotics was beneficial for improving the stability of the Cu(II)–antibiotic complex when lomefloxacin was used. Studies of the activity of the ternary complex in various *E. coli* strains showed that the coordinated species had the same activity as the free antibiotic, but the cell intake route appeared to be different in the two species [297].

Sparfloxacin is a fluoroquinolone antibacterial drug, which has been used to prepare a series of mononuclear Cu(II) complexes where the co-ligand was a terpyridine derivative [298]. These complexes were tested against *E. coli*, *P. aeruginosa*, *Serratia marcescens*, *B. subtilis*, and *S. aureus*, and they were more active than the free drug. All of the complexes exhibited the classical intercalative mode of binding, with DNA cleavage and a SOD-like activity. When sparfloxacin and its congener levofloxacin were associated with 1,10-phenanthroline, the resulting Cu(II) compounds were tested against the protozoan *Trypanosoma cruzi* and the activity was higher than benznidazole, which is the reference drug for this infectious agent [299]. A levofloxacin Cu(II) ternary complex with 1,10-phenanthroline was also tested against *E. coli*, where the

activity was analogous to that of the free drug, but the mechanism of the cell intake route involved different paths [300].

Another antibiotic drug where the Cu(II) complex was studied as an antifungal agent is amphotericin B, which was extracted from *Streptomyces nodosus* and it has been used for more than 50 years in the treatment of acute systemic fungal infections and protozoan pathogens with relatively rare resistance [301]. The rationale behind this study was that the activity of amphotericin B against *C. albicans* could be enhanced by the action of its copper complex together with the probable insertion of Cu(II) ions into the fungal cell membranes, which was demonstrated. The increased antifungal activity of the copper complex was not the sum of the toxic effects of the antibiotic and Cu(II) ions, but it was a consequence of the unique structure of the resulting compound.

Tobramycin and its copper complex have been demonstrated to have anti-inflammatory effects on phlogistic states related to cystic fibrosis. A series of experiments showed that tobramycin is active due to the spontaneous formation of a copper–tobramycin complex, which implies that copper–tobramycin may be a more effective therapy. Furthermore, this copper–antibiotic complex has a SOD-like activity [302].

Overall, these results demonstrate that copper complexes of antibiotics have comparable or higher activities compared with the free drugs, thus they could be exploited in antimicrobial therapies due to their different paths of cellular intake and different mechanisms of action.

8. Rhodium

The interest in rhodium as a potential anticancer metal dates back to the beginning of the 1970s when researchers focused their attention on dirhodium(II) complexes with bridging equatorial ligands, such as the typical dirhodium carboxylate $[Rh_2(RCOO)_4(solvent)_2]$ complex. This contains a Rh(II)–Rh(II) bond, four equatorial ligands in a lantern formation around the metal center, and an axial ligand on either end. Rh(II) ions are paramagnetic in a d^7 configuration and a diamagnetic complex forms following the pairing of the two unpaired electrons in the Rh(II)–Rh(II) bond. This type of compound has a carcinostatic activity, although it is much lower than that of cisplatin. A decade later, analogous compounds were found to be efficacious against Ehrlich ascites sarcoma and P 388 leukemia [303], but toxic effects prevented their use. More recently, Rh(II) citrate was reported to prolong survival and reduce the size of breast cancer carcinoma in mice when administered with maghemite NPs [304].

Research into rhodium complexes has progressed to include Rh(I) and Rh(III) mononuclear species. The former is isoelectronic where Pt(II) is a d^8 ion and its compounds seem to share some properties with cisplatin, such as DNA binding. Rhodium complexes do not represent an attractive topic for research into anticancer agents due to their kinetic inertness, although some unreactive compounds are active against tumors.

In general, rhodium has not captured the same level of interest as the other metals. Indeed, the published output during 2010–2013 was rather limited and there are few indications of improvements. Recent reviews have summarized the use of rhodium and iridium complexes together [305,306] or its use within the organometallic complexes of other noble metals [307].

8.1. Organorhodium(III) compounds

The most successful Rh(III) complexes used in anticancer studies are organometallic species. In fact, the inertness of Rh(III) can be overcome via the coordination of neutral arene or anionic (pentamethyl)cyclopentadienyl ligands. Cyclometalating pyridine or phenanthroline derivatives have also been employed. Organorhodium(III) compounds have been investigated in order to understand their mechanism of action, which appears to occur mainly via DNA interaction. For example, Barton's group studied Rh(III) metalloinsertors and found that they act by binding to DNA mismatches, by disrupting DNA synthesis, and they have IC50 values in the low micromolar range [308–310].

The synthesis and characterization of new bis-cyclometalated Rh(III) complexes containing dithiocarbamate derivatives flanked by two cyclometalated 2-phenylpyridines showed that intercalative binding occurred with calf thymus DNA due to the stacking between the 2-phenylpyridyl moiety and the base pairs of DNA [311].

In addition, the cyclopentadienyl ligand has attracted attention in the design of active Rh(III) species because the chemistry of cyclopentadienyl Rh(III) complexes is often considered to be similar to that of the effective anticancer agents, arene ruthenium(II) analogues. Like other arene ligands, cyclopentadienyl derivatives present a lipophilic protecting face to the metal by occupying three coordination sites at the octahedral metal center, while the remaining three sites allow the introduction of ligands with hydrophilic characters. Therefore, the careful tuning of both the lipophilic cyclopentadienyl derivative and the other coordinated ligands can modulate the solubility, the ligand-exchange kinetics, and the stability of the complexes. The results obtained with this type of compound have been reviewed recently [306].

Recently, it was found that pentamethylcyclopentadienyl-based rhodium complexes combined with hydroxypyrone (maltol and allomaltol) or piroxicamato ligands exhibited moderate to low cytotoxicity in different human cancer cell lines [312,313]. The antiproliferative activity of dinuclear di-(neutral) and tri-(cationic) thiolato-bridged pentamethylcyclopentadienyl Rh(III) complexes was evaluated using cisplatin-sensitive and -resistant cancerous human ovarian cell lines, i.e., A2780 and A2780cisR, respectively, as well as noncancerous human embryonic kidney cells [314]. The cationic complexes were particularly cytotoxic compared with the neutral ones, possibly due to the increased intracellular uptake of the former compared with the latter. The nature of the substituent attached to the thiolato-bridges appears to have a relatively strong influence on the cytotoxicity of the complexes, whereas the nature of the metal center is less important. The cytotoxicity of the complexes can reach the nanomolar range with elevated toxicity, particularly in cisplatin-resistant cell lines, thereby supporting the hypothesis that there is a different mechanism of action for this class of rhodium complexes compared to that of cisplatin.

8.2. Polypyridyl Rh(III) complexes

Analogous to Ru(II) compounds, Rh(III) complexes with polypyridyl co-ligands may also be active against cancer due to their ability to intercalate DNA. In fact, a variety of rhodium polypyridyl complexes bind DNA both covalently and non-covalently [315,316]. By increasing the surface area and hydrophobicity of the polypyridyl ligand, the cellular uptake of the drug improves, thereby resulting in increased cytotoxicity. These rhodium complexes appear to have anti-topoisomerase II activities and they act as photo-inducible agents.

8.3. Rh(I) carbene complexes

There have been few recent studies of the biological activity of Rh(I) compounds. However, it was reported that Rh(I) complexes containing 1,5-cyclooctadiene (COD) or carbonyl (CO) ligands possess anticancer activities against Ehrlich ascites, leukemia L1210, sarcoma 180, and metastatic lung cancer. The latest studies concern the cytotoxicity of a new organorhodium(I) complex

bearing both COD and *N*-heterocyclic carbene (NHC) ligands, which is cytotoxic to the colon cancer cell line HCT116 by targeting DNA, inhibiting metastasis, preventing cell division, and reducing DNA condensation [317]. Similar NHC Rh(I) complexes with COD or CO co-ligands were synthesized, which had pronounced antiproliferative activities and a moderate inhibitory activity on thioredoxin reductase (TrxR), and efficient binding to biomolecules (DNA and albumin). Moreover, changes in the mitochondrial membrane potential (MMP) were observed as well as DNA fragmentation in wild-type and daunorubicin- or vincristine-resistant Nalm-6 leukemia cells, thereby suggesting a complex mechanism of action for this type of complex, which are valid candidates as Rh(I)-based anticancer drugs [318].

9. Iridium

Iridium complexes have been studied extensively in recent years as novel agents for biomedical applications, including protein staining, cellular imaging, peptide labeling and chemotherapeutic drugs [319–324,305]. In the latter case, the literature does not reflect the same flourishing interest as that in the other noble metals and discussions of anticancer iridium compounds are often associated with analogous rhodium and/or osmium species that have the same reactivity. A probable reason could be the inertness of iridium, e.g., the lifetime for the exchange of an aqua ligand on $[Ir(H_2O)_6]^{3+}$ is about 300 years. However, the general kinetic inertness of iridium may be overcome by using appropriate ligands that facilitate the higher reactivity of the metal complexes: in fact, the reactivity of low-spin d^6 Ir(III) centers is highly dependent on the set of associated ligands.

The first attempts to assess iridium as an antineoplastic agent occurred shortly after the discovery of cisplatin. For almost 30 years, in an effort to replicate the same efficacy, investigations were focused on d^8 Ir(I) compounds with a square-planar geometry similar to cisplatin, such as [Ir(acac)(cod)] and its dinuclear analog $[IrCl(cod)]_2$, both of which have high activity, i.e., the former against mice Ehrlich ascites and Lewis lung carcinoma, and the latter has an antimetastatic activity in the Lewis lung model. At the turn of the millennium, the attention shifted to organoiridium(III) compounds, which exhibited promising antiproliferative activities against cancer cells, as well as other Ir(III) derivatives.

The strategies utilized for the design and development of bioactive iridium complexes as cytotoxic agents as well as their applications in medicinal inorganic chemistry have been reviewed recently [305]. This paper summarizes the most important work research in this field, which mainly involves the use of a stabilizing ligand, such as the pentamethylcyclopentadienyl anion, to increase the liability of *trans*-halide ligands. Additional strategies include complex formation with ligands that are cytotoxic by themselves via specific interactions with biological targets [[305] and references therein], or by modulating their redox activity [325].

In general, the ligands used most widely in the design of potentially active iridium complex are those leading to organoiridium species (arenes, cyclopentadienyl anion derivatives, and 2-phenylpyrydine derivatives) and polypyridyl compounds, or a combination of the two.

9.1. Half-sandwich organoiridium(III) complexes

During the writing of the present study, a review by Sadler appeared in the literature ahead of printing, which considered the half-sandwich organometallic Ir(III) cyclopentadienyl complexes [326]. Although this was outside the time span considered by this review, we found that it was of critical importance for the research field. The review considers Ir(III) organometallic compounds of the half-sandwich pseudo-octahedral pentamethylcyclopentadienyl type, which are the most widely studied anticancer agents based on this metal, and it reported their activities in different tumor lines and the relationships between their structure and activity. Their modes of action differ according to the ligands on the iridium centre, where some bind to DNA, whereas others can perturb the redox balance in cells [327], which probably also occurs via mitochondrial targeting, including primary redox mediation processes (ROS generation), subsequent DNA damage, and disruption of protein synthesis due to oxidative stress. Moreover, they can inhibit tumor necrosis factor α, promote DNA oxidation, and generate singlet oxygen when photoactivated. In addition, the mechanisms and pathways involved in their cellular internalization were investigated [328]. In fact, the mode of action of antitumor agents is a multi-step process that includes cell entry or accumulation, drug activation, binding to the cellular target, and the cellular responses to damage of the cellular target. Consequently, the efficient accumulation of metallodrugs in cancer cells is the first and critical step, which can lead to the success or not of a given complex.

9.2. Cyclometallated Ir(III) complexes

Another class of effective organoiridium complexes is based on cyclometallated ligands. These Ir(III) species have received considerable attention and they are important candidates for use as luminescent probes in cellular imaging because of their potential photophysical properties. They also have high cytotoxic activities. When 2-(2,4-difluorophenyl)pyridine was used as the ligand, good cytotoxicity against SP2 myeloma and Chinese hamster ovary cancer was detected based on blebs and vacuole formation in living cells within 30 min of exposure to the probe, which were indicative of apoptosis, but cell death was considerably faster under irradiation [329]. When the cyclometalating ligand was 2-phenylquinoline, the relative Ir(III) complex accumulated in mitochondria and induced mitochondrial shortening by conjugation with specific protein targets [330]. Using a derivative of 2-(5′-amino-4′-tolyl)pyridine containing three amino groups at the 5′-position, the relative Ir(III) compound could be photoactivated and it caused HeLa-S3 cell death by generating singlet oxygen in a pH-dependent manner after photoirradiation at 377 or 470 nm. The reactivity of this complex clearly depends on the pH, thus it can be used to stain acidic organelles, such as lysosomes [331].

In addition to being interesting catalysts for many organic and bioorganic reactions, iridium hydrides have also been the subjects of biological evaluations, which showed that they exhibited excellent anticancer effects on tumor cells [332]. Zhao et al. reported the synthesis and the properties of new cyclometalated iridium hydrides derived from the C—H bond activation of aromatic nitrones (based on the antioxidant α-phenyl-*N*-*tert*-butylnitrone structure), which exhibited a strong antiproliferative effect on human hepatocellular liver carcinoma cell line HepG2. The most promising iridium complexes exhibited strong interactions with DNA and subsequent conformational changes, where they were effective in vivo and they had reduced toxicity compared with cisplatin.

The association between cyclometalating ligands and polypyridyl with increasing conjugation (bipyridine, phenanthroline, and diphenylphenanthroline) affects the cytotoxic activity based on the simple model structure, $[Ir(ppy)_2(N\hat{N})]^+$, where ppy is the 2-phenyl-pyridine, by tuning its lipophilic nature versus its hydrophobic nature [333].

Although all three complexes have anticancer activities, that bearing the diphenylphenanthroline ligand had the highest cellular uptake efficiency and the greatest cytotoxic activity in several cancer cell lines at doses lower than cisplatin. The high cytotoxicity of this complex was related to its ability to localize in the cellular

membrane due to its strong hydrophobic character, thereby inducing endoplasmic reticulum stress and mitochondria-mediated apoptosis in human cancer cells. The main advantage of using these compounds is that they possess tunable luminescent properties, which allow more direct and accurate optical observations of their intracellular localization. The destination is the cytoplasm, where the cell death mechanism appears to begin.

Finally, organometallic bis-C,N-cyclometalated Ir(III) thiosemicarbazide complexes were tested by Ruiz and his group [334], which showed that these complexes have potent cytotoxic effects on breast cancer cells and they are up to 5-fold more active than cisplatin. Particularly remarkable is the very low resistance factor (RF in the range 0.9 and 1.1) of two of the characterized compounds against an A2780 cell line with acquired resistance to cisplatin, which efficiently overcame this problem. They also highlighted the capacity of the complexes to inhibit cathepsin B, an enzyme that is known to be overexpressed in several cancer cell lines, and their ability to bind human serum albumin protein (HSA), a transport agent for drugs. More recently, the same research group successfully synthesized a series of novel iridium benzimidazole cyclometalated complexes containing polyvalent ligands, which may have different and simultaneous functions [335]. These compounds exhibited good anticancer activities against several cancer cell lines. The representative complexes induced early and severe apoptotic mechanisms, exhibited good accumulation and S-phase cell arrest, and they bound HSA protein efficiently, whereas the binding to DNA in the minor groove was weaker.

10. Osmium

Osmium is the heavier congener of ruthenium and it is a metal that deserves the attention of researchers in the quest for new effective anticancer compounds. Research into osmium is rather recent but its complexes have become increasingly important in the field of tumor-inhibiting metal species since 2006, because several studies suggested them as interesting alternatives to their ruthenium analogues.

The early toxicology literature gave them the reputation of either being highly toxic (OsO_4) or relatively inert (Os(II) and Os(III) complexes), thus researchers overlooked their potential therapeutic applications until the synthesis of Os(II) arene complexes demonstrated that they have comparable cancer cell cytotoxicity to cisplatin [336,337]. The most recent trends in chemotherapeutic osmium compounds are based on the development of organometallic species, mainly with arene or cyclometallated ligands. Of course, other strategies include the synthesis of osmium analogues of successful ruthenium complexes [338], clusters [339], or higher oxidation states for the metal centre.

10.1. Osmium–arene complexes

In general, the limitation of arene complexes as metallodrugs is linked to their stability in water or air. The chemical reactivity (rate of hydrolysis, acidity of the aqua adducts, dynamic chelate ring opening, and interactions with nucleobases) of osmium arene complexes and its relationship to cancer cell cytotoxicity were controlled by the rational design of biologically active agents by varying the nature of the chelating ligands. This can be achieved by modulating the steric and electronic properties of the substituents on a chelating ligand to "fine-tune" the kinetics and thermodynamics of osmium drugs in aqueous media [340,341].

The in vitro and in vivo antitumor activities of a series of osmium arene complexes were evaluated [342–348]. No cross-resistance with platinum-based drugs was observed in cancer cells, such as the half-sandwich "piano-stool" Os(II) arene complexes [349]. These types of compounds may comprise a promising scaffold for drug design because variations in the arene ligand can modulate cellular uptake and DNA intercalation, and the ligands that represent the "legs" of the "piano-stool" can control reactivity and stability. Subtle changes in the structure of metal complexes can have a major effect on their biological activity, such as the surprising advantages of substituting the coordinated chloride by iodide in both iminopyridine and azopyridine complexes in the cellular metabolic pathways for organometallic Os(II) arene complexes [350]. This can be a way of addressing the problem of intrinsic or acquired resistance in chemotherapy.

10.2. Osmium complexes in high oxidation states

Metal complexes of osmium in low oxidation states of +2 [342–351,341,352–358] or +3 and +4 [359,338,360] have been shown to have anticancer properties by inducing cell death via DNA targeting, but a variety of high-valence antitumor drugs is also available: Os(VI) nitrido compounds with tridendate Schiff bases [361], with monodenate azole heterocycle ligands [362] or azopyridine complex [363], and one of the latest Os(VI) nitrido complexes bearing the 8-quinolinolato ligand and its derivatives [364]. Some of these complexes have higher cytotoxic potency compared with the commonly used clinical platinum-based chemotherapeutic drugs. Recently, the first osmium complexes to induce cell death via endoplasmic reticulum (ER) stress were synthesized. Lippard and coworkers obtained Os(VI) nitrido compounds bearing bidentate ligands and showed that small modifications to the ligand periphery induced completely different cellular responses, which ranged from genomic DNA damage leading to G2/M phase arrest and apoptosis, to ER stress, and culminating in p53-independent, caspase-directed apoptosis [365].

11. Rhenium

The use of rhenium complexes as anticancer drugs emerged only recently compared with others, i.e., at the beginning of the 2000s. They are normally Re(I) mono- or dinuclear hexacoordinated carbonyl species, where one or more heteroligands are bound in a mono- or polydentate fashion. Their mechanism of action is currently under study, but it seems to be connected to DNA interaction.

The ligands employed most widely in Re(I) compounds are diphosphines and polypyridyl species [366], which can be selected opportunely or derivatized for targeting toward cancer cells or mitochondria [367–371], because rhenium complexes normally have low selectivity. The latest trends also include the synthesis of fluorescent [372] or photo-activatable [373] Re(I) complexes.

A tricarbonyl Re(I) complex with thymidine as the co-ligand was found to be more potent than cisplatin [374,375]. It was expected that this compound would work by inhibiting the thymidine kinase 1 enzyme, but studies suggested that this might not be the only mechanism involved in its toxicity.

Rare examples of Re(IV) compounds with potent cytotoxic activity in vitro were reported by De Munno et al. [376]. All of the complexes had the general formula $ReCl_4L$, where L was 2,2′-bipyridine; 2,2′-bipyrimidine; 4,4′-dimethyl-2,2′-bipyridine; or 1,10-phenanthroline, and they all exhibited potent in vitro antiproliferative activities against a number of cancer cell lines.

The rhenium radioactive isotope, ^{188}Re, was used to prepare complexes with hydroxyethylidenediphosphonate, a bone growth regulator that can be used as a radiotherapeutic palliative in the treatment of bone cancer and metastasis [377–379]. Recent studies have reported improved survival and quality of life when

radiopharmaceuticals were given repeatedly or in combination with chemotherapy, with a significant reduction in pain.

12. Conclusions

In this review, we aimed to describe the surprisingly broad uses of noble metals and the importance of their compounds in the medical field. It is interesting that most of these metals have improved performance when they form complexes with different ligands, where they have higher activities than the free ligands.

Encouraging biomedical applications have also convinced researchers to study advanced classes of compounds with different ligands, and the literature is very rich and intense in this area. Although the applications of metal drugs are mainly related to the treatment of cancer, a significant amount of research has been conducted to obtain therapies for many other disorders. Indeed, metal complexes can be active against infections according to the same mechanisms as those implicated in the treatment of cancer. Thus, most of the metal compounds tested to determine their cytotoxicity in different tumor cell lines have also been assessed in terms of their antibacterial activity. Antibiotic compounds are often bound to a metal to enhance their efficacy or to avoid drug resistance. Therefore, metals in their elemental and coordinated states have been tested extensively to treat a wide range of diseases because they can act as antibiotic, antibacterial, antiviral, antimalarial, antitubercular, antileishmanial, antimycotic, antiarthritis, or anti-inflammatory agents.

Recently, biomedical researchers have discovered that metals can also be active in their elemental state as NP formulations. This field is fascinating because NPs are highly toxic against bacteria, particularly human pathogens, but they can also behave as transporters that carry drugs efficiently. However, despite the great number of articles published in this area in recent years, the uncertainty regarding their toxicity in humans has never been fully elucidated [380].

For all of these reasons, the noble metals considered in this review are attracting increasing interest in modern clinical medicine, where novel compounds are being developed that can combine therapeutic properties and reduced side effects by enhancing bioavailability and selectivity, which can also be achieved by using ligands that can behave as carriers. In general, given their low toxicity to humans, they have important roles in the treatment of diseases and they can provide the starting points for the design of future metal-based drugs to fight several serious diseases. Thus, the fight against cancer, bacteria, and infectious agents has gained many new allies.

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